

Anesthesia and Analgesia

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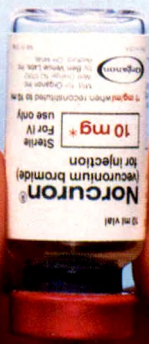


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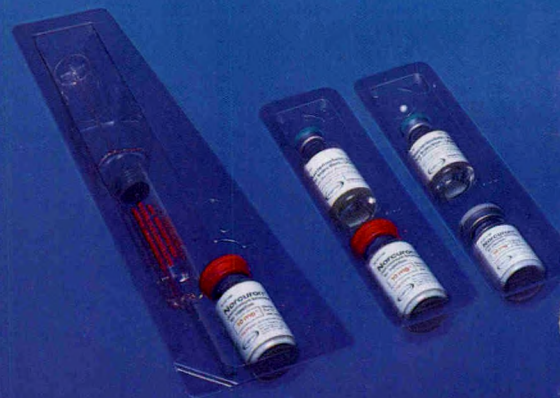
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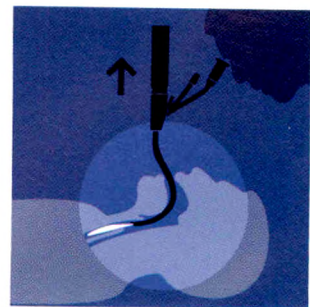
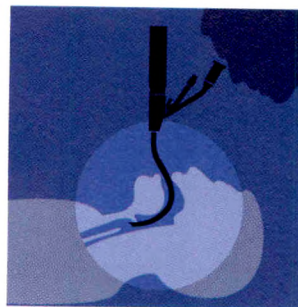
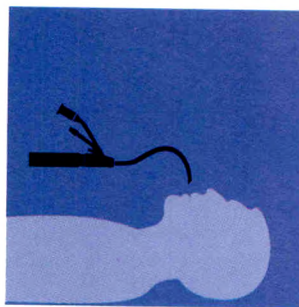
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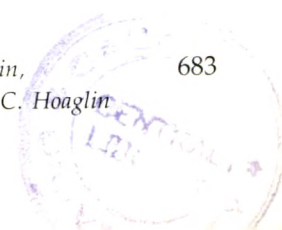
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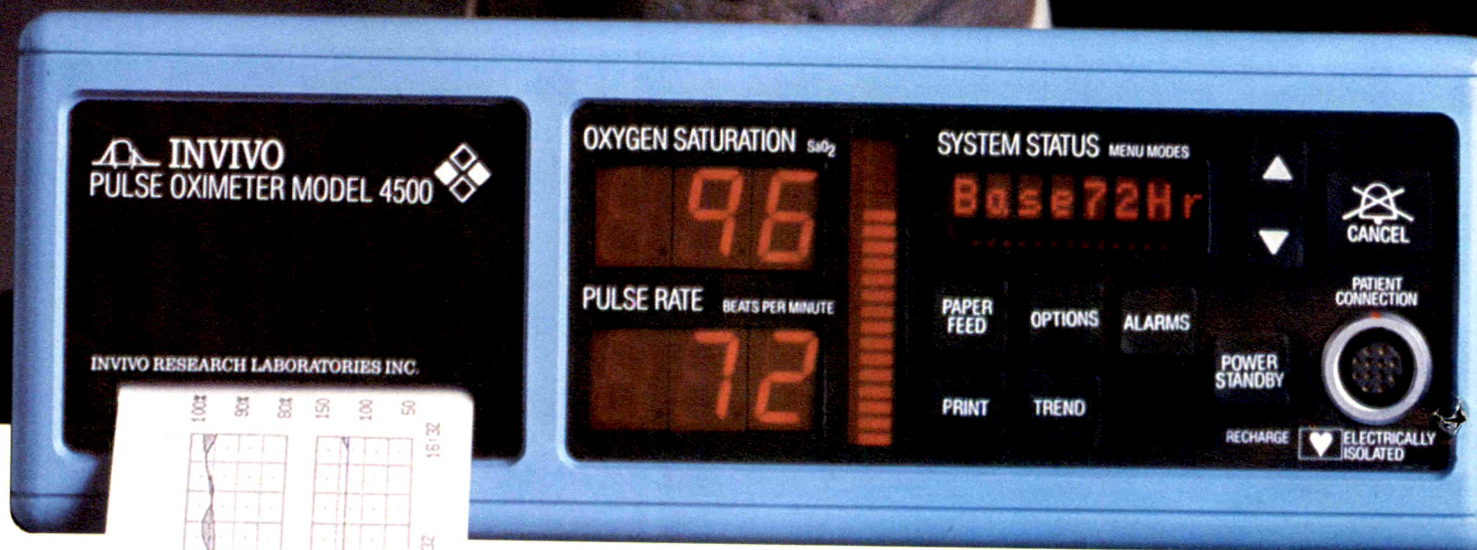
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SIEMENS



Anesthetic and Hemodynamic Effects of the Stereoisomers of Medetomidine, an α_2 -Adrenergic Agonist, in Halothane-Anesthetized Dogs

Ross G. Vickery, BS, Brett C. Sheridan, Ira S. Segal, MD, and Mervyn Maze, MB

VICKERY RG, SHERIDAN BC, SEGAL IS, MAZE M.

Anesthetic and hemodynamic effects of the stereoisomers of medetomidine, an α_2 -adrenergic agonist, in halothane-anesthetized dogs. *Anesth Analg* 1988;67:611-5.

The anesthetic-sparing and hemodynamic effects of the stereoisomers of the highly selective α_2 -adrenergic agonist medetomidine were studied in halothane-anesthetized dogs. Male beagles were anesthetized with halothane in oxygen. After a 2-hour equilibration period, halothane MAC and baseline hemodynamic functions were determined. DL- (n = 7), D- (n = 5), or L-medetomidine (n = 5) at 1, 3, and 10 $\mu\text{g/kg}$ was administered via a right atrial port over 15 minutes while each dog was given halothane at the MAC dose for that animal. Twenty minutes after the end of infusion (when the hemodynamic variables were stable), hemodynamic function was reassessed. Halothane MAC was then redetermined. MAC for halothane significantly

decreased after DL-medetomidine administration in a dose-dependent fashion to the extent that at the highest dose (10 $\mu\text{g/kg}$) the halothane MAC was $<0.1\%$. This effect could be mimicked by the D-isomer, whereas the L-isomer was without effect. Neither isomer changed the mean arterial pressure, whereas only the D-isomer significantly decreased heart rate and cardiac output. Medetomidine, the highly selective α_2 -adrenergic agonist, reduces the MAC for volatile anesthesia by a greater degree than with any other physiologic, pharmacologic, or pathologic intervention thus far reported. The fact that this effect is stereospecific suggests a structure activity relation that can be accounted for by a homogeneous receptor population. The role of medetomidine as a supplemental anesthetic agent appears promising and requires further investigation.

Key Words: SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—medetomidine. POTENCY, ANESTHETIC—MAC.

Clonidine, an α_2 -adrenergic agonist that inhibits central noradrenergic neurotransmission (1), reduces the dose requirements for anesthesia (2-6), and analgesia (7) during surgical stimulation. This anesthetic-sparing effect of clonidine may be due to a decrease in central release of norepinephrine (8), because manipulations that decrease central noradrenergic neurotransmission have been associated with a decrease in anesthetic requirements as reflected by a lower MAC (9).

Postsynaptic α_2 -adrenoreceptors have now been demonstrated in the central nervous system (10),

where they can mediate a sedative action (11) and thus could be a site for the MAC-sparing action of α_2 -agonists. It is also possible that the MAC-sparing effect of clonidine may be due to its antinociceptive properties (7) at the level of the spinal cord (12).

Clonidine may not be the most appropriate α_2 -adrenergic agonist for use in clinical studies, because a "ceiling effect" (3), followed by a reversal of the initial effect, occurs at higher doses (13). This property has been variously attributed to the mixed agonist-antagonist effect of clonidine at the α_2 -receptor (14) or to an α_1 -agonist effect (15). Medetomidine is a full agonist (16) that is more selective than clonidine for the α_2 -adrenoreceptor (17). Thus we expect medetomidine to be more efficacious in its anesthetic-sparing effect and also to be a useful probe for defining the mediating mechanism for this action of α_2 agonists.

In this study, we have used the racemate (DL-) and the individual stereoisomers (D and L) of medetomi-

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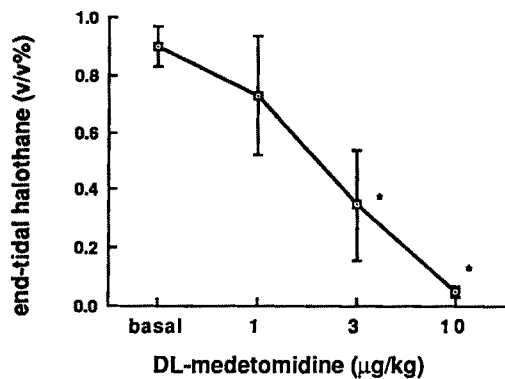


Figure 1. Effect of DL-medetomidine on halothane MAC. The MAC for halothane in oxygen was determined in dogs ($n = 7$) before (basal) and after DL-medetomidine 1, 3, and 10 $\mu\text{g/kg}$ IV. Data are presented as mean \pm SD. * $P < 0.05$.

dine to: 1) investigate the MAC-sparing action of medetomidine in halothane-anesthetized dogs; 2) characterize the hemodynamic effects of medetomidine during halothane anesthesia and; 3) define the active stereoisomer for the MAC-reducing and hemodynamic effects of medetomidine.

Methods

The study protocol was approved by the Animal Care and Use Committee at the Palo Alto VA Medical Center. Anesthesia was induced by mask inhalation of halothane in oxygen in male beagles (8–11 kg). After tracheal intubation, ventilation was controlled to maintain normocarbica ($\text{CO}_{2\text{ET}} = 4.5\%$). Catheters were inserted percutaneously for: 1) intraarterial blood gas determination and pressure recording (femoral artery); 2) pulmonary arterial and central venous pressure monitoring and cardiac output (thermodilution) assessment and; 3) intravenous fluid and drug administration. End-tidal halothane and CO_2 concentrations (infrared analysis), heart rate and rhythm (lead II of the ECG), systemic arterial pressure, central venous pressure, and pulmonary arterial pressure were continuously displayed and recorded. Core temperature was maintained at 37°C with insulating blankets and heating lamps. After a 2-hour equilibration period, the MAC for halothane was determined as previously described (18) and baseline hemodynamic function (mean arterial blood pressure, heart rate, central venous pressure, pulmonary arterial diastolic pressure, pulmonary artery occluded pressure, cardiac output, and derived systemic vascular resistance) was assessed. Medetomidine in the DL- ($n = 7$), D- ($n = 5$), and L- ($n = 5$) forms were administered in separate experiments at each of three doses (1, 3, and 10 $\mu\text{g/kg}$) via the right atrial

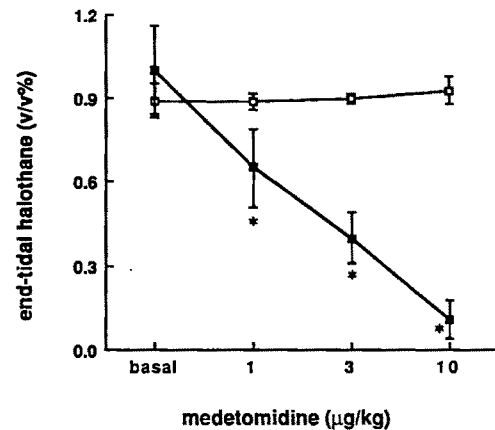


Figure 2. Effect of D- (■) or L- (□) medetomidine 1, 3, and 10 $\mu\text{g/kg}$ IV on halothane MAC. Data are presented as mean \pm SD. * $P < 0.05$.

port over 15 minutes while maintaining the dog at its individual MAC for halothane. Ten minutes after the termination of the infusion (at which time the profile was stable), hemodynamic function was reassessed. Also at this time, arterial blood was sampled for measurement of gas tensions and acid/base status. MAC determination was then repeated after which the next dose of medetomidine was given and the cycle repeated. Data were compared by ANOVA for repeated measurements and subsequently by paired t -test with Bonferroni correction. A P value of <0.05 was considered the level for statistical significance.

Results

Halothane MAC

After DL-medetomidine administration, the MAC for halothane progressively decreased such that at the highest dose, the anesthetic requirement was decreased by more than 90% (Fig. 1). The MAC-sparing effects of DL-medetomidine could be duplicated with the D-stereoisomer, whereas the L-isomer was without effect on the sensitivity of the dogs to anesthesia with halothane (Fig. 2).

Hemodynamic Effects of Medetomidine

At 1.0 MAC halothane, DL- and D- medetomidine administration resulted in a progressive decrease in heart rate (Fig. 3) and cardiac output (Fig. 4) whereas the L-form was without effect on the cardiovascular system. Mean arterial, central venous, and pulmonary arterial pressures were unaffected by medetomidine administration. Although the derived systemic

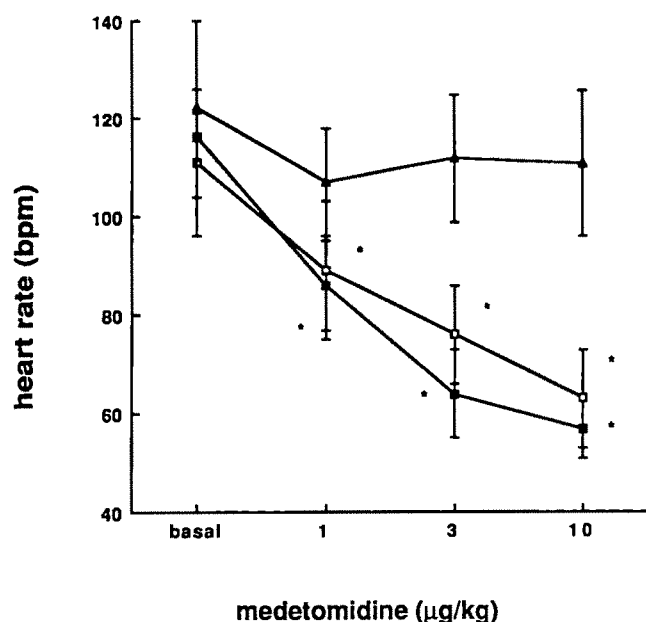


Figure 3. Effect of D-medetomidine on heart rate in halothane-anesthetized dogs at 1 MAC before (basal) and after DL- ($n = 7$, \square), D- ($n = 5$, \blacksquare), or L- ($n = 5$, \blacktriangle) forms of medetomidine 1, 3, and 10 $\mu\text{g/kg}$ IV. Data are presented as mean \pm SD. * $P < 0.05$.

vascular resistance tended to increase after medetomidine administration, this did not achieve statistical significance.

Discussion

Three major results follow from this study. First, medetomidine caused a dose-dependent decrease in halothane MAC. Second, mean arterial blood pressure did not change, but heart rate and cardiac output decreased progressively with the dose of medetomidine administered. And last, each of these actions was due to the D-stereoisomer of medetomidine with the L-isomer having little influence on these parameters.

Mechanism for the Anesthetic-Sparing Effect of Medetomidine

Medetomidine, the highly selective α_2 -adrenergic agonist, reduces MAC for volatile anesthesia substantially more than does any other physiologic, pharmacologic, or pathologic intervention thus far reported. Indeed, at the highest dose (10 $\mu\text{g/kg}$), the volatile anesthetic could be discontinued for more than 1 hour with no purposeful response to tail-clamping. In each case the animal could be promptly aroused with the specific α_2 -adrenergic antagonist, idazoxan (1

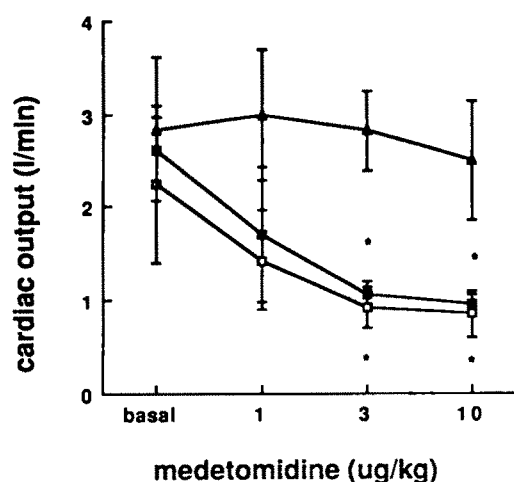


Figure 4. Effect of medetomidine on cardiac output (thermodilution technique) in halothane-anesthetized dogs at 1 MAC before (basal) and after DL- ($n = 7$, \square), D- ($n = 5$, \blacksquare), or L- ($n = 5$, \blacktriangle) forms of medetomidine 1, 3, and 10 $\mu\text{g/kg}$ IV. Data are presented as mean \pm SD. * $P < 0.05$.

mg/kg). The fact that this effect is stereospecific suggests a structure activity relation that can be accounted for by a homogenous receptor population.

α_2 -Adrenergic receptors are located presynaptically (19) on postganglionic neurons in the peripheral sympathetic nervous system and also centrally in noradrenergic pathways. In the presence of agonists these receptors decrease norepinephrine release (20). Manipulations that decrease central noradrenergic neurotransmission are associated with a decrease in anesthetic requirements as reflected by a lower MAC (9). Furthermore, when central norepinephrine-containing pathways are completely disrupted by neurolytic (21) or neurotoxic lesions (22), the MAC for volatile anesthetic is reduced by as much as 35%. Although we did not measure central norepinephrine release, it is unlikely that the putative inhibitory effect of medetomidine on central noradrenergic neurotransmission (17) is enough to explain the >90% reduction in MAC that was seen in these experiments because MAC is reduced no more than 40% when noradrenergic pathways are completely disrupted (21,22).

α_2 -Adrenergic receptors are also located postsynaptically in the central nervous system (10), although their precise function at this site is not well understood (11). α_2 -Adrenergic agonists hyperpolarize locus coeruleus slices in the rat (23) by increasing K^+ conductance (24). Nicoll and Madison have suggested that general anesthesia is characterized by hyperpolarization through an increase in K^+ conductance and consequent depression of neuronal excitability (25). Thus it is possible that α_2 -adrenergic agonists supplement the anesthetized state by such

an action at postsynaptic sites in the central nervous system.

Hemodynamic Effects of Medetomidine at 1 MAC Halothane

Although mean arterial pressure was unaffected, there was a progressive decrease in heart rate and cardiac output concomitant with a tendency for the systemic vascular resistance to increase in sympathetically denervated dogs (26) and rats (27), the central hypotensive action of α_2 -adrenergic agonists is not seen. Conversely in the sympathetically denervated animal, an increase in systemic vascular resistance may result by virtue of the vasoconstrictive effect mediated by postsynaptic α_2 -adrenoreceptors located extrajunctionally in the peripheral vasculature (28). However, volatile anesthetics, especially halothane, may blunt the α_2 -mediated vasoconstriction response (29). This may explain the lack of change in systemic arterial, central venous, and pulmonary arterial pressures after medetomidine administration in halothane-anesthetized animals. We speculate that in the functionally sympathectomized halothane-anesthetized dogs (30,31) neither the centrally mediated hypotensive effect nor the peripherally mediated hypertensive effect is seen. Medetomidine decreases heart rate dose dependently (32). Both a centrally mediated vagomimetic effect and a sympatholytic action are possible causes of the bradycardia (33), although our study did not distinguish between these two possible mechanisms.

There are many possible reasons for the decrease in cardiac output that occurred in this study. First, the bradycardic response might have resulted in a progressive decrease in cardiac output. Second, the modest increase in afterload could have contributed in part to the decrease in cardiac output. Last, we speculate that the oxygen requirements, and hence cardiac output, might have decreased as anesthetic depth was increased with medetomidine. At lower doses of medetomidine, relatively modest changes in cardiovascular parameters were seen, suggesting that clinical trials to evaluate medetomidine as a supplement to general anesthesia can be conducted. Because we have characterized the active enantiomer of the racemate, we believe serious consideration should be given to performing early clinical studies with the pure D-enantiomeric form of medetomidine. There may well be major differences in the pharmacologic profile and pharmacokinetics of the enantiomeric forms that we were not able to identify in our system.

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A Comparison of the Antinociceptive and Behavioral Effects of Intrathecally Administered Opiates, α -2-Adrenergic Agonists, and Local Anesthetics in Mice and Rats

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OSSIPOV MH, SUAREZ LJ, SPAULDING TC. A comparison of the antinociceptive and behavioral effects of intrathecally administered opiates, α -2-adrenergic agonists, and local anesthetics in mice and rats. *Anesth Analg* 1988;67:616-24.

This study was undertaken to compare the antinociceptive and behavioral effects of intrathecally administered opiates, α -2-adrenergic agonists, and local anesthetics injected by lumbar puncture in the mouse and rat. Antinociception was determined by observing the response to a clamp applied to the tail (Haffner test) of the mouse and by the rat tail-flick test; log dose-response curves for antinociception were generated for each drug in each test. Motor coordination and other behavioral effects were also observed. Morphine and fentanyl (μ -opiate agonists) as well as ethylketocyclazocine (EKC) and U50488H (κ -opiate agonists), together with buprenorphine (partial μ -opiate agonist) and the α -2-adrenergic agonist clonidine, all produced antinociception in both species without causing significant behavioral or motor dysfunctions at antinociceptive doses. Xylazine (also an α -2-adrenergic agonist), ketamine, procaine, and lidocaine inhibited responses but only at doses that also produced motor impairment or paralysis. Nalbuphine (mixed opiate agonist-antagonist) was without any effect in both species. These data suggest that the μ - and κ -opiate agonists and clonidine are the preferred agents for producing antinociception without compromising motor function.

Key Words: ANALGESICS, INTRATHECAL—morphine, fentanyl. ANESTHETIC TECHNIQUES—spinal. SYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—clonidine.

Regional anesthesia is produced by the intrathecal injection of a local anesthetic. In addition to eliminating nociceptive input, however, this means of producing anesthesia also eliminates nearly all sensory input, sympathetic outflow, and motor output, resulting in cardiovascular changes and somatic motor paralysis (1). Recent studies (2-6) indicate that the intrathecal injection of opiate analgetics produces clinically useful relief of pain without loss of either ambulation or sympathetic nervous activity (7). Side effects have been seen after intrathecal morphine administration, however, including delayed respiratory depression, pruritis, and urinary retention (7). The occurrences of the untoward effects in humans are also dose dependent and occur at doses greater than those required to elicit analgesia (8); therefore,

the intrathecal administration of opiates remains a clinically useful means of pain relief.

Data exist to indicate that agonists of various opiate receptor subtypes produce different degrees of pain relief, depending on the nociceptive stimulus present. Thus, κ -receptors preferentially mediate visceral pain, whereas μ and δ -opiate receptors mediate cutaneous thermal pain (4,5). In addition to the opiates, intrathecally administered α -2-adrenergic agonists also produce antinociception in a number of species (9,10). The present study was undertaken to compare the antinociceptive and behavioral effects of opiates, α -2-adrenergic agonists, and local anesthetics administered intrathecally in mice and rats.

Methods

Separate groups of male Swiss-Webster mice (weight, 10 to 20 g) and male Sprague-Dawley rats (weight, 50 to 75 g) were used in all experiments. In each experiment, six rats were used for each data point, and no rat was injected more than once. All experiments

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described in this paper were approved by our Animal Care and Use Committee.

Rat Tail-Flick

The rat tail-flick test, a modification of that described by D'Amour and Smith (11), was performed by placing the tail of a rat under a focused (2-mm × 4-mm) radiant heat source (Analgesiameter, IITC, Landing, NJ) that was activated simultaneously with a timer. When the radiant heat stimulus became painful to the animal, the rat flicked its tail aside, uncovering a photocell and shutting off both lamp and time. Control tail-flick latencies were determined to the nearest 0.1 second for each rat twice before drug injection. Post-treatment tail-flick latencies were determined 1, 2.5, 5, and 10 minutes after injection. A maximum exposure (cut-off latency) of 10 seconds was used to prevent tissue damage. The maximal effect observed at each dose was used in the construction of dose-response curves.

Naloxone Reversal

In separate groups of rats, 1 mg/kg, IP of naloxone was injected 15 minutes before the intrathecal injection of morphine, ethylketocyclazocine (EKC), U50488H, or ketamine. Dose-response curves and A_{50} values in the presence of the antagonist were determined as described earlier.

Mouse Haffner Assay

The mouse Haffner assay was originally described by Haffner (12) in 1929 and modified by Takagi et al. (13). The assay was performed by applying a serrefine artery clip that delivered a force equivalent to a weight of 400 g applied to the base of the tail of a mouse. A nociceptive response was defined by a biting of the clip or surrounding area by the mouse. Control response latencies were determined once for each mouse before injection. Post-treatment biting latencies were determined 1, 2.5, 5, and 10 minutes after injection. A cut-off latency of 15 seconds was used. The maximal effect observed at each dose was used in generating the log dose-response curves.

Behavioral Effects

The rats were observed for signs of overt behavioral effects such as catalepsy, ataxia, or paralysis.

Injection Technique

The intrathecal injections were performed according to the method of Hylden and Wilcox (14). The rat was held firmly by the pelvic girdle. A 30-gauge needle attached to a 25- μ l Hamilton Syringe was inserted into the tissue on one side of the L5 or L6 spinous process at an angle of about 20°. The needle was advanced into the groove between the spinous and transverse processes and then moved forward into the intervertebral space at an angle of about 10°. About 0.5 cm of the needle was then in the vertebral column. Correct placement of needle was indicated by an arching of the tail. Drugs were dissolved in saline or water and administered in a volume of 5 μ l.

Statistical Analysis

The degree of antinociception was defined as the percentage of maximum possible effect (% MPE) in both the mouse Haffner assay and rat tail-flick tests and was calculated as

$$\frac{(\text{post-treatment latency} - \text{control})}{(\text{cut-off latency} - \text{control})} \times 100.$$

The latencies were 10 and 15 seconds for the rat tail-flick and mouse Haffner tests, respectively. The % MPE was determined for each dose at each time period measured, and the largest value obtained with each dose was plotted against the log dose. A regression line was calculated by a method of least squares, as were the A_{50} values (dose that produced 50% MPE) and the 95% confidence limits. The slopes of each regression line with the 95% confidence limits and Student's *t*-values were calculated and used when testing for parallelism. All statistical calculations were performed by computer programs described by Tallarida and Murray (15).

Results

Opiate Analgesics

Fentanyl, morphine, ethylketocyclazocine (EKC), U50488H, and buprenorphine produced dose-dependent antinociception in the mouse Haffner assay. The slopes of the dose-response curves were not significantly different (Fig. 1). The rank-order potency was described as fentanyl = morphine >> EKC > buprenorphine > U50488H >> ketamine >> nalbuphine = 0. Potency ratios were obtained by dividing the A_{50} of a compound by that of fentanyl, which was 0.1 μ g. The potency ratios for the opiates tested were 1

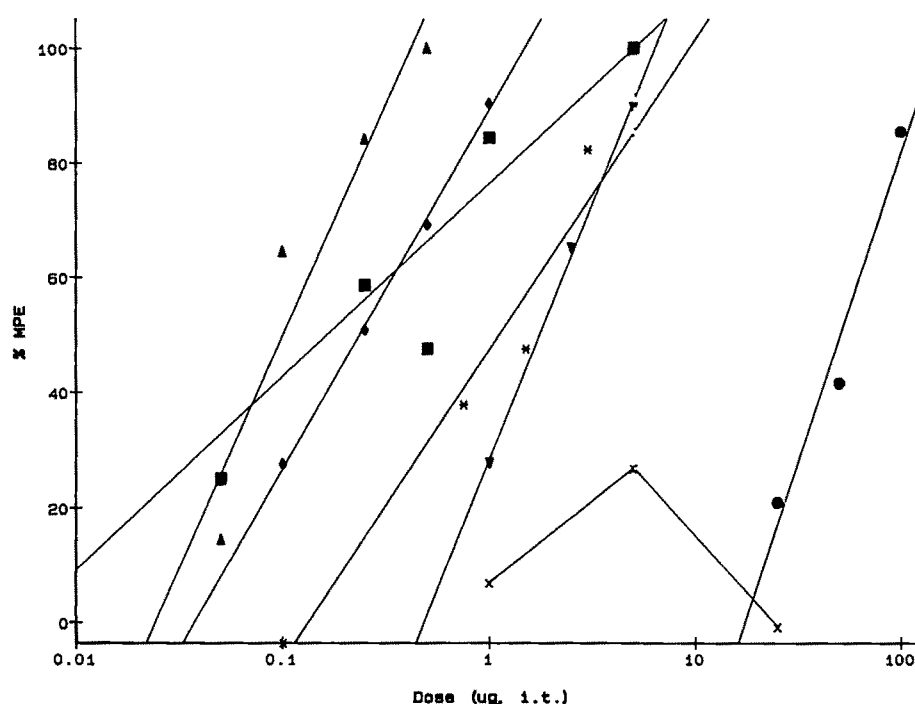


Figure 1. The dose-related increases in clip biting latency in the mouse after intrathecal (IT) injection are represented as % MPE (see text) for buprenorphine (*), EKC (◆), fentanyl (▲), ketamine (●), morphine (■), nalbuphine (x), and U50488H (▼). The regression lines for buprenorphine, EKC, fentanyl, morphine, nalbuphine, and U50488H did not deviate from parallelism. Ketamine did not appear to show dose-related increases in biting latency; rather, hind limb ataxia and paralysis appeared at higher doses.

Table 1. Summary of Potencies of Intrathecally Administered Drugs Assessed in the Mouse Haffner Test*

Drug (n)	A ₅₀ (95% confidence limits)	Slope (95% confidence limits)	r
Opiates			
Buprenorphine(30)	1.12 (0.44–2.83)	54 (16–92)	0.97
EKC(24)	0.24 (0.21–0.26)	62 (54–70)	1.00
Fentanyl(24)	0.10 (0.04–0.26)	81 (2–159)	0.95
Ketamine(18)	50.7 (11.5–222.7)	107 (–173–388)	0.98
Morphine(36)	0.10 (0.03–0.43)	34 (10–57)	0.89
Nalbuphine(24)	NA	NA	
U50488H(18)	1.75 (1.21–2.52)	89 (43–134)	1.00
α-2-Adrenergic agonists			
Clonidine(24)	14.9 (10.5–21.0)	86 (52–120)	0.99
Xylazine(24)	12.1 (3.6–40.4)	86 (–37–208)	0.93
Local anesthetics			
Lidocaine(18)	26.2 (21.1–32.5)	114 (71–157)	1.00
Procaine(30)	25.4 (14.0–46.0)	94 (25–164)	0.97

*The A₅₀ doses (in μg producing 50% MPE) and slopes are derived from the regression lines for the appropriate log dose-response curves. Abbreviations: NC, A₅₀ not calculated because either motor or behavioral effects interfered with testing; NA, no activity in the dose range tested; n, number of animals used.

(morphine), 2.4 (EKC), 11 (buprenorphine), 17 (U50488H), and 51 (ketamine). Ketamine inhibited the biting response only at doses that produced gross motor impairment. Ataxia was observed after the injection of 50 μg, and dragging of the hind limbs occurred after the injection of 100 μg ketamine. Nalbuphine did not produce any analgetic activity at any dose tested (maximum of 25 μg). The calculated A₅₀ doses for the active analgetic agents are shown in Table 1.

Results similar to those seen in the mouse were obtained in the rat tail-flick test, except that the

potency of morphine relative to that of fentanyl was greatly reduced. The slopes of the dose-response curves were not significantly different (Fig. 2).

The rank-order potency for the opiates was fentanyl >> buprenorphine > EKC > morphine > U50488H >> ketamine = nalbuphine = 0. Potency ratios were obtained by dividing the A₅₀ of a compound by that of fentanyl, which was 0.36 μg. The potency ratios for the opiates tested were 16 (buprenorphine), 17 (EKC), 25 (morphine), and 45 (U50488H). Ketamine raised tail-flick latencies above the control levels, but this effect, not dose-depen-

Figure 2. The dose-related increases in tail-flick latency in the rat after intrathecal (IT) injection of buprenorphine (*), EKC (◆), fentanyl (▲), ketamine (●), morphine (■), nalbuphine (x), and U50488H (▼) are represented as % MPE (see text). The regression lines for buprenorphine, EKC, fentanyl, morphine, and U50488H did not deviate from parallelism. Ketamine did not appear to show dose-related increases in biting latency; rather, hind limb ataxia and paralysis appeared at higher doses. Nalbuphine did not produce any significant changes in tail-flick latency or in behavior.

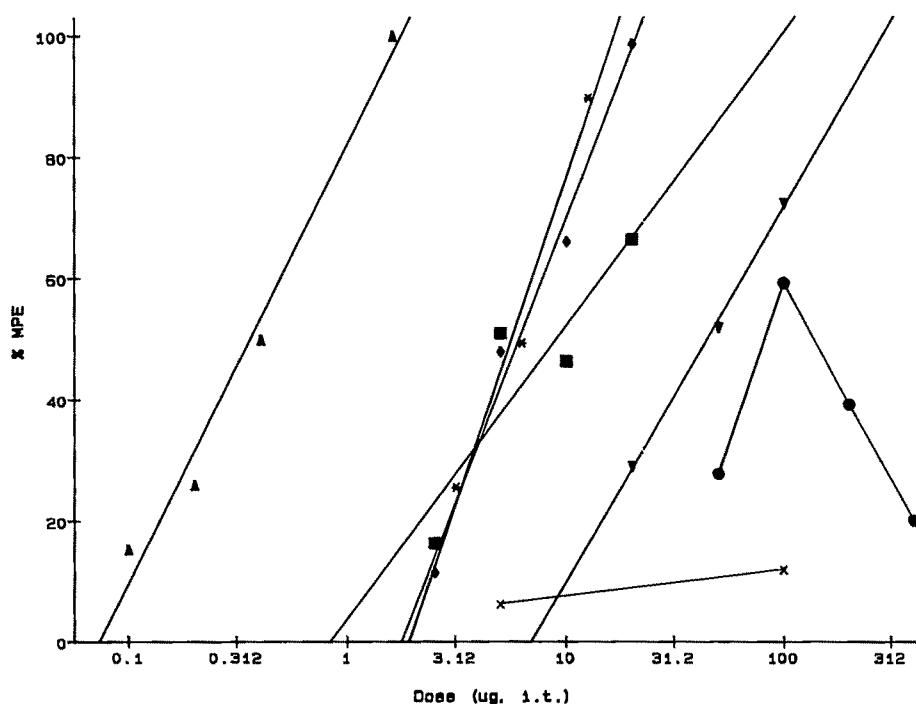


Table 2. Summary of Potencies of Intrathecally Administered Drugs Assessed in the Rat Tail-Flick Test*

Drug (n)	A ₅₀ (95% confidence limits)	Slope (95% confidence limits)	r
Opiates			
Buprenorphine(24)	5.62 (1.89–16.7)	106 (–95–308)	0.99
EKC(24)	6.09 (4.54–8.15)	93 (58–127)	0.99
Fentanyl(24)	0.36 (0.23–0.56)	72 (41–103)	0.99
Ketamine(24)	NC	—	—
Morphine(24)	8.99 (2.65–30.5)	48 (–24–121)	0.90
Nalbuphine(24)	NA	NA	—
U50488H(18)	44.6 (30.2–65.7)	62 (25–98)	1.00
α-2-Adrenergic agonists			
Clonidine(18)	46.1 (4.53–469)	96 (–292–484)	0.95
Xylazine(36)	6.44 (2.88–14.4)	32 (19–46)	0.96
Local anesthetics			
Lidocaine(18)	NC	—	—
Procaine(18)	NC	—	—

*The A₅₀ doses (in μ g producing 50% MPE) and slopes are derived from the regression lines for the appropriate log dose-response curves. Abbreviations as in Table 1.

dent, was complicated by the presence of concurrent motor effects. The greatest antinociceptive effect occurred at 100 μ g and was diminished after the administration of 400 μ g. Ataxia produced by ketamine progressed to hind limb paralysis as the dose was increased. Nalbuphine, given in doses of up to 100 μ g, produced no significant changes in tail-flick latencies. The dose-response curves are illustrated in Figure 2 and the potencies (A₅₀) are summarized in Table 2.

The antagonistic activity of naloxone (1 mg/kg, IP) given 15 minutes before the spinal opiate injection

was tested against morphine, EKC, ketamine, and U50488H (Table 3). The antinociceptive effect of morphine was markedly reduced by pretreatment with naloxone. The maximum effect was 42% MPE with 100 μ g, whereas morphine alone produced 66% MPE with only 20 μ g. Doses of morphine >100 μ g were not well tolerated by the rats, producing a violent scratching and biting behavior, and therefore were not tested. Thus, because the greatest response seen in the presence of naloxone was <50% MPE, the A₅₀ was not calculated, as it would lie outside the range of doses tested. The antinociceptive effect of EKC was

Table 3. Naloxone Inhibition of the Antinociceptive Effect of Ethylketocyclazocine (EKC), Morphine, and U50488H in the Rat Tail-Flick Test*

	Morphine	EKC	U50488H
No naloxone			
A ₅₀	8.99	6.09	44.6
95% confidence limits	2.65-30.5	4.54-8.15	30.2-65.7
Slope	48	93	62
95% confidence limits	-24-121	58-127	25-98
n	24	24	18
r	0.90	0.99	1.00
After naloxone			
A ₅₀	Not calculated†	27.8	34.3
95% confidence limits		8.00-97.0	31.6-37.1
Slope		118	94
95% confidence limits		-137-372	84-104
n	18	18	24
r		0.99	0.99

*Naloxone, 1 mg/kg, was administered intraperitoneally 15 minutes before IT opiate.

†At the highest dose of morphine (100 μ g), the maximal effect was 42% MPE after naloxone; thus, no A₅₀ dose was calculated (see Results). Naloxone raised the A₅₀ dose of EKC but did not change that of U50488H.

also attenuated by naloxone. The A₅₀ in the presence of naloxone was 28 μ g, a 4.5-fold increase from its A₅₀ when administered alone. The antinociceptive potency of U50488H was not changed by naloxone pretreatment. The A₅₀ of U50488H in the presence of naloxone was 34 μ g and was not significantly different from the A₅₀ value of 44 μ g obtained without naloxone. The slopes of the dose-response curves of both EKC and U50488H were not significantly different from the slopes of the curves obtained in the presence of naloxone. Naloxone pretreatment had no effect on either the antinociceptive or the ataxic effect of ketamine.

α -2-Agonists

Clonidine produced an antinociceptive effect after IT injection in the mouse and had an A₅₀ value of 15 μ g (Table 1). Xylazine produced considerable motor dysfunction and paralysis at the same doses that inhibited the biting response. Its A₅₀ dose was 12 μ g.

In the rat tail-flick test, both clonidine and xylazine produced dose-dependent elevations in response latencies. Clonidine had an A₅₀ of 46 μ g (Table 2), and some hind limb ataxia was observed at the higher doses employed. Xylazine was more potent than clonidine and had an A₅₀ of 6 μ g (Table 2), but it also reduced motor activity at doses eliciting a lower degree of analgesia than did clonidine.

The dose-related antinociceptive effects of cloni-

dine and xylazine for the mouse Haffner assay and the rat tail-flick test are illustrated in Figure 3.

Local Anesthetics

Procaine and lidocaine were equieffective in the mouse Haffner assay. The A₅₀ of lidocaine was 26 μ g and that of procaine was 25 μ g (Table 1). Both agents produced dose-dependent inhibition of the biting response concurrent with paralysis of the hind limbs. The slopes of the dose-response curves were not statistically different (Fig. 4).

Both lidocaine and procaine increased tail-flick latencies at lower doses. As the doses increased and paralysis became more complete, however, tail-flick latencies either did not increase any further (procaine) or actually decreased (lidocaine) (Fig. 4); thus, no A₅₀ was calculated for these drugs in the rat tail-flick test.

Behavioral Effects

The intrathecal administration of high (25 μ g) doses of morphine produced a violent scratching reaction in mice accompanied by vocalization and biting of the injection site. Further, the mice were very sensitive to tactile stimuli and became aggressive when touched. This reaction to morphine, which was not attenuated by naloxone, was not produced by any other drug tested.

The σ -opiate agonist ketamine produced an antinociception only when motor dysfunctions were also present. Lidocaine and procaine produced increasing degrees of ataxia and paralysis as the dose was increased in both mice and rats. Clonidine and xylazine elicited ataxia in mice at high doses. Fentanyl, EKC, nalbuphine, buprenorphine, and U50488H did not produce any motor or behavioral effects at the doses tested. A summary of the observed behavioral effects appears in Table 4.

Discussion

The ability of opiates to produce antinociception when administered intrathecally has been demonstrated in a number of species, including humans [see (16)]. The data presented in this paper reaffirm this analgetic activity of opiate analgetics when administered by the intrathecal route. Further, the importance of the blood-brain barrier in determining the potency of an opiate analgetic is underscored. In the

Figure 3. The dose-related changes in the mouse Haffner test (open symbols) or the rat tail-flick test (filled symbols) after the intrathecal injection of clonidine (circles) or xylazine (triangles) are presented. The regression lines derived from the mouse Haffner test do not differ from parallelism, whereas those derived from the rat tail flick do.

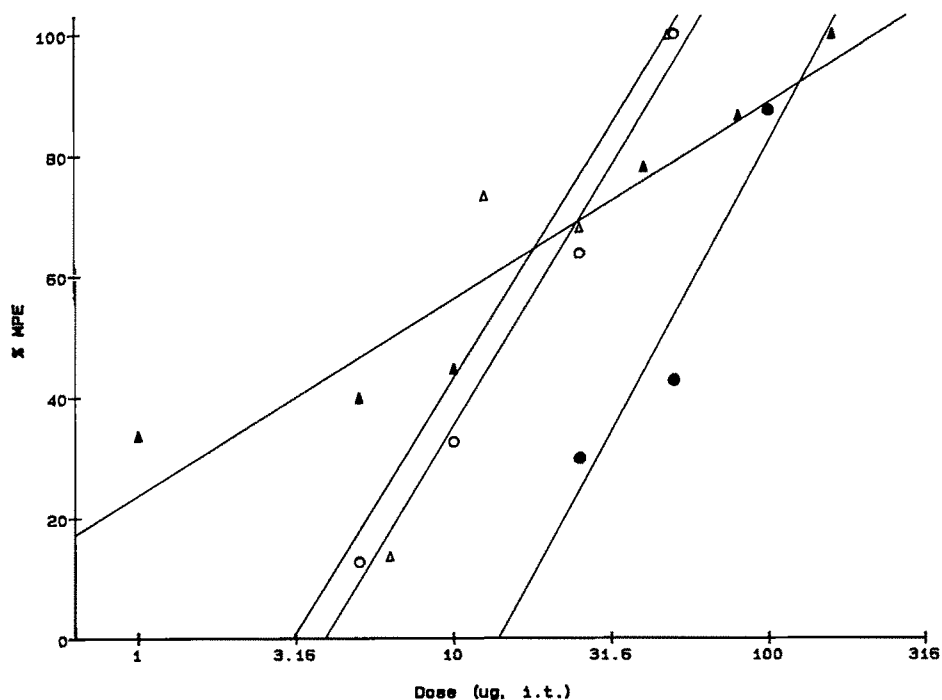
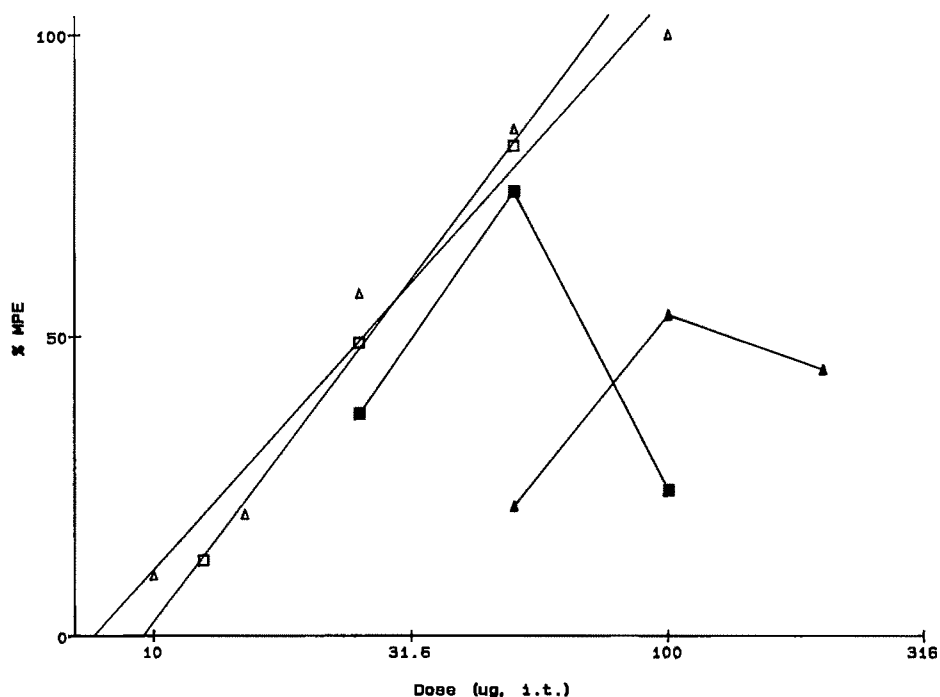


Figure 4. The dose-related changes in the mouse Haffner test (open symbols) or the rat tail-flick test (filled symbols) after the intrathecal injection of lidocaine (squares) or procaine (triangles) are presented. The regression lines derived from the mouse Haffner test do not differ from parallelism. Both local anesthetics did not produce dose-dependent increases in tail-flick latency; rather, tail-flick latency decreased with the highest doses tested.



clinical situation, fentanyl administered epidurally (8) or systemically is about 100 times more potent than morphine. In our studies the potencies of fentanyl and morphine were within one order of magnitude when administered IT. These results are similar to those reported by Durant and Yaksh. Early studies by Kutter et al. (17) showed that fentanyl owes its great

potency to its high lipophilicity: because when fentanyl and morphine are both administered on the brain side of the blood-brain barrier, their potencies are quite similar, whereas fentanyl is two orders of magnitude more potent than morphine when administered outside of the blood-brain barrier.

In both the mouse Haffner (mechanical nocicep-

Table 4. Behaviors Observed after IT Administration of Opiates, α -2-Adrenergic Agonists, and Local Anesthetics

Drug	Mouse	Rat
Opiates		
Buprenorphine	Decreased motor activity	Decreased motor activity
EKC	Straub tail*	Piloerection
Fentanyl	Ataxia, straub tail*	Ataxia, rigidity
Ketamine	Hind limb paralysis	Hind limb paralysis
Morphine	Ataxia, straub tail,*	
	Allodynia, increased motor activity	Increased motor activity
Nalbuphine	No observed effect	No observed effect
U50488H	No observed effect	No observed effect
α -2-Adrenergic agonists		
Clonidine	Ataxia, rearing, aggression, piloerection	Ataxia, piloerection
Xylazine	Hind limb paralysis	Ataxia, ptosis
Local anesthetics		
Lidocaine	Hind limb paralysis	Hind limb paralysis
Procaine	Hind limb paralysis	Hind limb paralysis

*Concurrent tonus of flexor and extensor muscles of the tail, causing a characteristic sigmoidal-shaped tail in rodents commonly seen after opiate administration.

tion) and rat tail-flick (thermal nociception) models, the opiate agonists produced dose-dependent antinociception. A report by Schmauss et al. (5) suggested that different opiate receptor subtypes may modulate pain produced by different stimuli. In that report, cutaneous thermal pain was ablated by μ - and δ -, but not κ -opiate receptor activation while chemically induced pain was ablated by spinal μ - and κ -, but not δ -opiate receptors. Our findings regarding the responses to thermally produced painful stimuli do not agree with this observation. Both μ and κ , including the highly κ -specific agonist U50488H (18), produced antinociception in both the mechanical and cutaneous thermal pain models. In our study, however, the relative potency of U50488H was reduced markedly in the tail-flick test. Thus, while U50488H was an effective antinociceptive agent in the tail-flick test, its relative potency (compared with fentanyl) was very low. Fentanyl was 12 times more potent than U50488H in the mouse Haffner assay and 124 times more potent in the rat tail-flick test. These data suggest that the κ -agonist was considerably less active relative to fentanyl in the thermal nociceptive test. Although the possibility that the difference in the potency of κ -agonists may have been influenced by the species as well as test employed should be considered, the influence of species difference may be partly reduced by referring the potency ratios to a standard (i.e., fentanyl) within each species.

Because the activity of morphine and EKC, a κ -agonist with some μ -opiate activity [cf. (5)], were reduced by naloxone, and because naloxone preferentially binds to the μ - rather than κ -opiate receptor (18), it is likely that these agents exerted their activity at the μ -opiate site. The activity of U50488H, however, was not reduced by the dose of naloxone used,

suggesting that its effect was independent of the μ -opiate site. κ -Opiate-mediated antinociception against thermal stimuli has also been described by others (16,19). It appears that spinally administered κ -opiates do indeed attenuate heat-produced pain but do so at a reduced level of activity when compared with chemically or mechanically induced nociception.

The partial μ -opiate agonist buprenorphine also produced dose-dependent antinociception in the mouse and rat nociceptive models. Nalbuphine, a mixed κ -agonist/ μ -antagonist, failed to produce an antinociception in either the rat tail-flick or mouse Haffner assays. The ineffectiveness of nalbuphine after spinal injection in rats has been reported earlier and reflects the weak analgetic activity of the drug (5).

Ketamine was chosen as representative of the σ class of opiate receptors because it has been used clinically. Although presently there is considerable discussion regarding the proper classification of σ - and phencyclidine (PCP) agonists, ketamine may be considered as a σ -opiate agonist because it produced (+)-N-allylnormetazocine [(+)-NANM]-like discriminative stimuli in rats, and (+)-NANM is a σ -opiate ligand (20). Although we have shown that ketamine altered responses to nociception after intrathecal injection, this effect has only occurred when motor impairment became obvious or gross behavioral toxicity was present. Earlier reported studies in the rat also indicated that intrathecal ketamine inhibited tail withdrawal from hot water but also produced histopathologically detected damage to the spinal cord, thus limiting its potential clinical utility as a spinally administered analgesic (21). The motor effect of keta-

mine did not appear to be opiate-receptor mediated, as naloxone did not alter its activity.

The contribution of the α -2-noradrenergic system to spinally mediated antinociception is well documented. Systemically administered clonidine inhibits the tail-flick reflex in spinalized mice (22), and intrathecally administered clonidine produces dose-dependent inhibition of the tail-flick reflex in lightly anesthetized (10) and conscious (9) rats. The intrathecal injection of an α -2-antagonist diminishes supraspinal stimulation-produced antinociception (23) and the antinociceptive effect of supraspinally administered morphine (24). The data presented in this paper further support the involvement of α -2-adrenoceptors in the modulation of thermal and mechanically evoked nociception by showing that intrathecally administered α -2-agonists produce an antinociception in mice and rats. In addition to inhibiting nociceptive responses, xylazine, an α -2-agonist, also used as a veterinary sedative/anesthetic agent, produced a considerable degree of ataxia in both mice and rats after intrathecal administration. This effect was not seen with clonidine. It is likely that the paralysis seen after xylazine administration was not related to its α -2-adrenergic activity but is unique to this compound.

In contrast to the opiate agonists, local anesthetics produced an ablation of the responses to nociception only when the loss of motor activity was present. The loss of sensory and motor activity after intrathecal administration of lidocaine and procaine has been well documented [see Reference 1]. It is interesting that the intrathecal injection of a local anesthetic did not completely abolish the tail-flick reflex of the rat, even in those with bilateral paralysis of the hind limbs. A hyperreflexive response to a pinching of the tail (25) or a tail-flick stimulus (2) after lumbosacral block was reported to be present after the intrathecal or epidural administration of bupivacaine. Moreover, muscle tone and nociceptive reflexes remained unchanged in dogs with bilateral hind limb block produced by epidural injections of bupivacaine (unpublished observations). This seemingly paradoxical effect might be due to the local anesthetic, although not having reached motor neurons responsible for the tail-flick reflex (e.g., if the injection was made too far rostrally), being able to interfere with a tonic descending inhibition of the spinal nociceptive reflex. The fact that a reflex arc (i.e., tail flick) is still active in the presence of bilateral hind limb paralysis argues in favor of this explanation. Data to support this interpretation are found in experiments that showed that producing a reversible high (C-1) spinal blockade increased the responsiveness of dorsal nociceptive

neurons of cats to nociceptive stimuli (26). The effect seen in that study was attributed to an interruption of the tonic descending inhibitory influences arising from supraspinal sites. Thus it is possible that a local anesthetic can produce a segmental block, ablating a descending modulatory influence on the spinal nociceptive reflex at caudal sites. Alternatively, it may be that the reflex arc involving the tail is especially resistant to local anesthetics.

Allodynia, a nociceptive reaction to a stimulus that is normally not nociceptive, was seen in the mouse after the intrathecal administration of high doses of morphine. This reaction had been described by Yaksh et al. (27) in rats and cats. It is not believed to be opiate-receptor-mediated, because naloxone exacerbated rather than attenuated this response. Further, it appears that only compounds that undergo considerable glucuronidation show this effect; other opiates, such as meperidine and fentanyl, do not. In our studies, the only compound that produced allodynia was morphine. Other behavioral responses not mediated by opiate receptors have been observed after the intrathecal administration of opiates. Dynorphine-A, a κ -opiate agonist, produced hind limb flaccidity and paralysis that was not opiate-receptor-mediated in the rat (28). Watkins et al. (29) reported convulsions produced by intrathecally administered high doses of morphine and catalepsy that was only partially blocked by naltrexone. Because intrathecally administered drugs may cause unpredictable behavioral effects not related to the receptor systems associated with the injected agent, the interpretation of these behavioral effects should be approached with caution. Further, the effects produced by a few agonists of a receptor subtype may not always reflect the behavioral effects mediated by that receptor subclass but may be due to unique properties of the drug used.

In summary, this study showed that both the rat tail-flick and mouse Haffner models provide reliable indicators of antinociceptive activity of intrathecally administered compounds. μ -Opiate agonists retained their antinociceptive potency in both tests, whereas κ -specific agonist lost a significant degree of activity in the thermal test.

The results obtained in these studies indicate that of the analgetic agents available for spinal analgesia, the μ - and κ -opiate agonists and the α -2-agonist clonidine are the most favorable in that these agents may be expected to produce analgesia without the concurrent development of motor or behavioral side effects.

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Potency of Succinylcholine at the Diaphragm and at the Adductor Pollicis Muscle

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SMITH CE, DONATI F, BEVAN DR. Potency of succinylcholine at the diaphragm and at the adductor pollicis muscle. *Anesth Analg* 1988;67:625-30.

To quantify the differential effect of succinylcholine at the diaphragm and the adductor pollicis muscle, 10 patients were studied during halothane-nitrous oxide anesthesia. Train-of-four stimulation was applied to the ulnar and phrenic nerves. The force of contraction and the electromyographic response of the adductor pollicis were measured and compared with the diaphragmatic electromyogram. Then dose-response curves for both muscles were constructed using incremental doses of succinylcholine with an infusion to replace metabolized or redistributing drug. Linear regressions were obtained between the logit transformation of neuromuscular blockade at the adductor pol-

licis and diaphragm and the logarithm of the dose. The diaphragm was relatively resistant to succinylcholine. At 90% adductor pollicis block, the diaphragm was only (mean \pm SEM) $37 \pm 3\%$ blocked. The diaphragm required 1.8 ± 0.2 times as much succinylcholine as the adductor pollicis for an identical 90% block. The ED_{50} and ED_{90} values for succinylcholine at the diaphragm were 0.23 ± 0.04 and 0.40 ± 0.09 mg/kg, respectively. Corresponding values for the adductor pollicis were 0.14 ± 0.01 and 0.21 ± 0.02 mg/kg. The data indicate that the degree of adductor pollicis blockade might overestimate the intensity of diaphragmatic paralysis.

Key Words: MONITORING—electromyography, phrenic nerve stimulation, train-of-four.
NEUROMUSCULAR RELAXANTS—succinylcholine.

Compared with peripheral muscles, respiratory muscles are more resistant to the action of nondepolarizing neuromuscular blocking agents (1-9). The degree of respiratory sparing associated with the administration of depolarizing muscle relaxants is not known. Foldes et al. (10) reported that the administration of small doses of succinylcholine to unanesthetized subjects produced very little respiratory sparing compared with *d*-tubocurarine. Their measurements consisted of vital capacity and grip strength. In contrast, Williams and Bourke (11) found that in unanesthetized subjects, respiratory strength (as measured by maximum inspiratory and expiratory pressure or forced vital capacity) was spared compared with grip strength during a succinylcholine infusion. However, both of these studies involved the measurement of the activity of the entire respiratory system. Among

the respiratory muscles, the diaphragm appears to be the most resistant to nondepolarizing blockers (8). The present study was designed to compare dose-response relations of the depolarizing muscle relaxant succinylcholine at the diaphragm and adductor pollicis muscles by stimulating the nerves supplying them.

Methods

The protocol was approved by the Hospital Ethics Committee, and all patients gave informed consent. Ten ASA physical status I or II adults undergoing elective surgical procedures were studied. All patients were free from neuromuscular, renal, hepatic and electrolyte disorders, and were not taking any medication known to or suspected of interfering with neuromuscular function. Premedication was with IM morphine 0.1 mg/kg and atropine 0.006 mg/kg 1 hour before the anticipated surgical procedure. After application of an automatic blood pressure cuff and ECG, anesthesia was induced with thiopental 3-5

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mg/kg and fentanyl 1–2 $\mu\text{g/kg}$. The patients' lungs were ventilated by bag and mask with increasing concentrations of halothane (0.5–1.5% end-tidal, measured with a mass spectrometer) and nitrous oxide 66%. End-tidal Pco_2 was maintained between 30 and 35 mm Hg. Tracheal intubation was performed after topical application of 4% lidocaine, 2 mg/kg. Anesthesia was maintained with halothane 0.2–0.4% end-tidal and nitrous oxide 66% in oxygen. Ventilation was adjusted to maintain end-tidal Pco_2 between 30 and 35 mm Hg (mass spectrometer) using a semi-closed circle system with a CO_2 absorber.

The ulnar nerve was stimulated supramaximally at the elbow according to the method of Ali et al. (12). Train-of-four (TOF) was repeated every 12 seconds using square wave pulses of 0.2 ms duration at a frequency of 2 Hz. A Grass S88 stimulator and a SIU5 isolation unit were employed. The hand and forearm were immobilized in a splint. The evoked force of contraction of the adductor pollicis muscle was measured with a Grass FT10 force displacement transducer and recorded on paper. Electromyograms (EMG) were recorded from two silver–silver chloride electrodes placed on the dorsum of the hand in the first digital interspace and at the base of the proximal phalanx of the third finger (13). An indifferent electrode was placed nearby.

The right phrenic nerve was stimulated supramaximally with silver–silver chloride electrodes positioned in the neck near the posterior border of the sternocleidomastoid muscle as previously described (3). The EMG response of the diaphragm to TOF stimulation (2 Hz) delivered at 12-second or greater intervals was recorded through three surface electrodes positioned at the eighth intercostal space. The EMG signals were amplified, filtered (bandwidth 3 Hz–1 KHz), and displayed on a storage oscilloscope (3, 13). After a stable baseline had been obtained, cumulative doses of succinylcholine were administered until at least 95% depression of the diaphragmatic EMG relative to control. Each dose increment was given only after the effect of the previous dose had reached a stable response defined as two equal consecutive adductor pollicis twitch or EMG responses. To allow for the rapid elimination of succinylcholine during the period of administration of incremental doses, an infusion of the drug was started once the effect from the initial dose had reached a stable response (14).

The rate of infusion to replace metabolized or redistributed drug was determined as follows: the ED_{90} of succinylcholine has been established at 0.22–0.30 mg/kg (14–16), and the dose to maintain 90% blockade by infusion is 1.70–4.68 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$

(17–19). Assuming linear pharmacokinetics, the rate of elimination should be proportional to the dose given. Thus, the hourly rate to maintain 90% blockade is approximately 15 times the ED_{90} , and the hourly rate at which succinylcholine should be administered to compensate for elimination is 15 times the dose already given. Therefore, when the maximum effect from the first dose (0.15 mg/kg) was observed, a second dose (0.1 mg/kg) was administered together with an infusion, at an hourly rate equal to the first dose times 15 (2.25 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$). When the maximum effect from the second dose was apparent, a third incremental dose (0.1 mg/kg) was given, and the infusion was set at 15 times the first two doses (3.75 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$). Thus, the infusion rate increased linearly with the amount of drug already given. Only the dose given in bolus form was considered in the calculations of dose-response curves, because the amount given by infusion was administered only to compensate for losses. This method has been shown to yield dose-response curves for succinylcholine similar to those obtained with a single bolus technique (14).

Twitch augmentation due to repetitive firing is common after administration of depolarizing muscle relaxants (13,20–22). When TOF stimulation is used, this phenomenon is usually present on the first mechanical twitch response (T1) and virtually absent on the fourth (T4). However, the amplitude of the electrical response is not affected by repetitive firing (13). For this reason, dose-response curves were calculated using both mechanical T4 and electrical T1 responses for the adductor pollicis muscle, and electrical T1 response for the diaphragm compared with their respective prerelaxant control values. Linear regressions were obtained between the logit transformation of neuromuscular block and log dose using the method of least-squares analysis (23). A regression line was calculated for each patient, from which a mean dose-response curve was constructed. The slope of the curves and effective doses for 50% and 90 block (ED_{50} and ED_{90}) were derived from the curves and compared between muscles using paired Student's *t*-test. The potency ratio between the diaphragm and the adductor pollicis was determined. In addition, twitch tension response (T4 relative to control) was compared with the electromyographic response (T1 relative to control) for the adductor pollicis muscle using linear regression of the logit transformation of neuromuscular block. The results are expressed as mean values with the standard error of the mean (SEM) as an index of dispersion. $P < 0.05$ was considered significant.

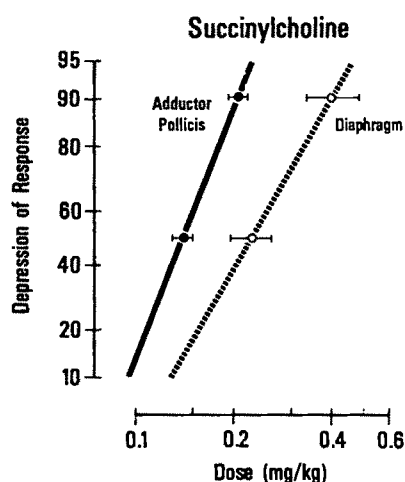


Figure 1. Mean cumulative dose-response curves for succinylcholine at the diaphragm (first response/control—EMG), the adductor pollicis (fourth twitch/control—twitch tension) muscles. The logit transformation of neuromuscular blockade is plotted against the logarithm of the dose. The lines were obtained by linear regression. Error bars represent SEM.

Table 1. Effective Dose (mg/kg) of Succinylcholine to Produce 50% (ED₅₀) or 90% (ED₉₀) Neuromuscular Block of the Diaphragm and Adductor Pollicis Muscle in 10 Adults*

	Diaphragm	Adductor pollicis	Ratio diaphragm/adductor pollicis
ED ₅₀	0.23 ± 0.04†	0.14 ± 0.01	1.61 ± 0.15
ED ₉₀	0.40 ± 0.09†	0.21 ± 0.02	1.81 ± 0.22

*Values are means ± SEM.

†P < 0.05 between muscles (paired Student's *t*-test).

Results

A total of four men and six women was studied. The mean age was 51 ± 5 years, mean weight was 68 ± 3 kg, and mean height was 169 ± 3 cm. Three to six doses were required to complete the study in each individual patient. Maximum blockade occurred within 1.5–2 minutes after the first dose and 1.0–1.5 minutes after the subsequent doses. All measurements were completed within 5–10 minutes.

Comparisons between dose-response curves at the diaphragm (EMG) and adductor pollicis (twitch tension) revealed that the diaphragm was relatively resistant to succinylcholine (Fig. 1), with statistically different potency estimates (Table 1). There were no significant differences between slopes (diaphragm = 4.73 ± 0.42 vs adductor pollicis = 5.80 ± 0.39 , $0.05 < P < 0.10$). At 90% twitch depression of the adductor pollicis, the diaphragm was only $37 \pm 3\%$ blocked and approximately 1.6–1.8 times as much succinylcholine was required at the diaphragm as at the

Table 2. Comparison between Potency Estimates for Succinylcholine at the Adductor Pollicis Using Mechanical (Twitch Tension—T4) or Electrical (EMG—T1) Responses in Five Patients

	Mechanical	Electrical†
ED ₅₀ (mg/kg)	$0.12 \pm 0.01^*$	0.12 ± 0.01
ED ₉₀ (mg/kg)	0.19 ± 0.01	0.18 ± 0.01

*There were no significant differences between the two methods.

†Values are means ± SEM.

adductor pollicis muscle for a similar degree of block (Table 1). Comparisons between mechanical (twitch tension—T4) and electrical (EMG—T1) responses of the adductor pollicis were obtained in five patients. These data revealed an excellent correlation between the two methods ($r = 0.97$). Derived values between the two methods were correspondingly similar in these five patients (Table 2). There was no evidence of development of phase II block (defined as T4/T1 ratio < 0.5) in any patient.

Discussion

The present study demonstrates that the diaphragm is relatively resistant to the action of the depolarizing muscle relaxant, succinylcholine. This diaphragm sparing effect is comparable to previously reported results for nondepolarizing muscle relaxants (1–9). The results also agree with those of Williams and Bourke (11) who found that in 10 healthy, unanesthetized volunteers, respiratory strength was spared compared with grip strength during an infusion of succinylcholine. When mean grip strength was reduced to 50% of control, maximal inspiratory pressure, maximum expiratory pressure, and forced vital capacity were 86%, 78%, and 86% of control values, respectively. Similarly, Jorgensen et al. (24) found respiratory sparing with the depolarizing muscle relaxant decamethonium in human volunteers. In addition, diaphragmatic sparing has been documented with decamethonium (21,22), and succinylcholine (25) in the intact cat, and with decamethonium in a guinea pig muscle preparation (26). However, Foldes et al. (10) reported only a relatively small degree of respiratory sparing with succinylcholine. In their study, when succinylcholine 80 $\mu\text{g/kg}$ was given to conscious volunteers together with the selective plasma cholinesterase inhibitor hexafluorenum, the subjects experienced an almost identical decrease in vital capacity as in grip strength (52 and 69%, respectively). However, subjects given *d*-tubocurarine 100 $\mu\text{g/kg}$ in their study had a 6-fold decrease in grip strength compared with vital capacity (77 vs 12%

decrease, respectively). However, these results may have been influenced by the use of hexafluorenum which, in addition to its pseudocholinesterase-inhibiting actions, may exhibit weak nondepolarizing neuromuscular blocking properties (27).

In the present study, comparisons were made between mechanical responses at the adductor pollicis and electrical activity at the diaphragm. Stimulating the phrenic nerve allows the response of the diaphragm only to be observed. This has the advantage of being independent of the function of the respiratory system as a whole, so that the diaphragm may be isolated from other muscles of the respiratory system that exhibit varying degrees of sensitivity to neuromuscular blocking agents (5,8,28,29). The EMG of the diaphragm was measured because of its independence of respiratory mechanical parameters such as lung or chest wall compliance, which may alter the geometry of the respiratory system as compared with transdiaphragmatic pressure measurements. In the five patients who had simultaneous mechanical and EMG recordings of their adductor pollicis response, the correlation between twitch tension and EMG was excellent, with derived potency estimates that were nearly identical. The use of the mechanical T4 as an index of neuromuscular blockade is justified here because the total dose of succinylcholine given (0.5 mg/kg) was much less than the amount associated with phase II block (5-7 mg/kg) (13,19).

Cumulative dose-response techniques are well suited to study the potency of neuromuscular blocking agents because fewer patients are required to obtain statistically valid comparisons. This permits the study of a muscle relaxant's effects on one or more muscles of differing sensitivities at a variety of dosage levels in the same patient (30). Therefore, the problem of whether to include or reject neuromuscular responses of 0 and 100%, which are occasionally produced by single doses, is avoided. The chief limitation of the cumulative dose-response technique is the requirement that redistribution and metabolism be negligible during the period of administration of incremental doses. This assumption holds true for the longer acting nondepolarizing relaxants *d*-tubocurarine and pancuronium (31). However, for the intermediate acting relaxants atracurium and vecuronium, cumulative dose techniques may underestimate potency (32-35). Thus, the addition of an infusion to replace metabolized or redistributed drug would enhance considerably the usefulness of these techniques. Previous studies demonstrated the validity of the cumulative dose with infusion technique for atracurium and vecuronium (36), as well as for succinylcholine (14).

It has been documented that onset of and recovery from a single dose of succinylcholine 0.8 mg/kg occurs earlier at the diaphragm than at the adductor pollicis muscle in patients under thiopental-nitrous oxide-fentanyl anesthesia (37). Vanderwater et al. (38) similarly observed that awake adult males given 20 mg succinylcholine (approximately 0.28 mg/kg) experienced cessation of respiration that preceded paralysis of limbs. However, return of respiration was later than was return of muscular activity of the limbs. Whereas the earlier onset in both studies may possibly be due to increased diaphragmatic blood flow favoring faster access of succinylcholine to the postsynaptic acetylcholine receptor, the earlier recovery in one study (37) may represent diaphragmatic resistance. The fact that Vanderwater et al. (38) observed peripheral limb movements well before resumption of respiratory movements may indicate the multiplicity of factors that are required for adequate respiratory function including the intercostal muscles and muscles of the upper airway such as pharyngeal, laryngeal, and jaw muscles, all of which may exhibit differing sensitivities to neuromuscular blocking agents (5,8,28,29).

While it has long been known that respiratory muscles are more resistant to nondepolarizing relaxants than are peripheral muscles, the etiology of this respiratory-sparing effect remains unclear. Proposed mechanisms include different types of receptor, number of receptors, amount of neurotransmitter released with each stimulus, or quantity of acetylcholinesterase. Lu (39), using external electrodes to measure depolarization of the isolated guinea pig diaphragm, latissimus dorsi, and serratus anterior muscles, demonstrated that the affinity of agonists and antagonists for the acetylcholine receptor was the same for all muscles, suggesting that the diaphragm does not have a different receptor type. If the diaphragm end-plate contained a greater number of receptors than peripheral muscle, then the diaphragm should be more sensitive to a depolarizing muscle relaxant such as succinylcholine. Because the present study has demonstrated that this is not the case, it is more likely that the relative resistance of the diaphragm to neuromuscular blocking agents is due to increased release or decreased breakdown of acetylcholine at the diaphragmatic neuromuscular junction.

The monitoring of neuromuscular function during anesthesia and surgery serves as a valuable guide to relaxant administration. The use of a relatively sensitive muscle such as the adductor pollicis may offer certain advantages. When full recovery of the adductor pollicis muscle has occurred, one can assume that no residual diaphragmatic paralysis exists. However,

adequate intubating conditions are present when all muscles, including the diaphragm, are paralyzed. This requires much more than the ED₉₀ for the adductor pollicis. At this dose, 0.21 mg/kg, there is little diaphragmatic blockade (37%). Thus, monitoring the adductor pollicis function is of limited value in the assessment of intubating conditions. Assuming that the diaphragm is typical of muscles that are resistant to succinylcholine, a dose of 0.4 mg/kg would be expected to produce more than 90% blockade in only half the patients. Considering interindividual variability, it is not surprising that excellent intubating conditions are not obtained reliably unless at least 1 mg/kg of succinylcholine is administered, or four to five times the adductor pollicis ED₉₀.

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Intranasal Nitroglycerin and Intraocular Pressure during General Anesthesia

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MAHAJAN RP, GROVER VK, SHARMA SL, SINGH H. Intranasal nitroglycerin and intraocular pressure during general anesthesia. *Anesth Analg* 1988;67:631-6.

Two separate studies of the effects of nitroglycerin (NTG) on intraocular pressure (IOP) were conducted. In study I, 12 healthy adults received 3 ml NTG solution (2 mg/3 ml) intranasally during steady-state anesthesia. This resulted in a significant decrease in IOP along with decreases in arterial blood pressure and central venous pressure. In study II, 30 patients, classified randomly into two equal groups, received either normal saline (3 ml) or NTG solution (2 mg/3 ml) intranasally, in a double-blind manner, 2 minutes before anesthetic induction with thiopental followed by succinylcholine (1.5 mg/kg). In patients given

saline, IOP increased significantly above the preinduction levels after succinylcholine. Tracheal intubation increased it further. In the NTG group, increases in IOP after succinylcholine and after tracheal intubation were significantly less than in the control (saline) group. It is concluded that intranasal administration of NTG decreases IOP in anesthetized patients and, when employed as pretreatment, allows the use of succinylcholine to facilitate tracheal intubation without an increase in IOP above preinduction levels.

Key Words: EYE—*intraocular pressure.*
PHARMACOLOGY—*nitroglycerin.*
NEUROMUSCULAR RELAXANTS—*succinylcholine.*

Rapid-sequence induction of anesthesia for patients with penetrating eye injuries continues to be a matter of concern because no clear and reliable methods for avoiding increases in intraocular pressure (IOP) have been agreed upon (1). Succinylcholine, the relaxant of choice for rapid intubation (2), causes a transient but significant increase in IOP (3,4). IOP is further increased after tracheal intubation (5). Several methods of pretreatment have been suggested (6-10), but none has been found to be consistently and completely effective in preventing succinylcholine-induced increases in IOP (1,11-15).

Nitroglycerin (NTG; IV infusion) decreases IOP in normal volunteers and in patients with open-angle or narrow-angle glaucoma (16). We have measured the effect of nitroglycerin (intranasal) on IOP during steady-state anesthesia (study I). In addition, we have evaluated its role in preventing IOP increases

associated with succinylcholine and tracheal intubation (study II).

Methods

Two separate studies were conducted. The declaration of Helsinki was respected, and all procedures followed were in accord with the standards of the Ethical Committee of our institute. Informed consent was obtained from all the patients.

Study I

Twelve patients, scheduled for elective surgery unrelated to the eye, were studied. They were 20-45 years old, weighing 57.5-82 kg, ASA physical status 1, and had no eye ailments. Premedication was with morphine 0.1 mg/kg and promethazine 0.4 mg/kg IM 1 hour before anesthesia. On arrival in the operating theatre, ECG leads, blood pressure cuff, and peripheral venous lines were placed. An infusion of 5% dextrose was started and maintained at a constant

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rate of $3 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ during the study. A cubital vein was cannulated percutaneously with a long 16-g catheter for central venous pressure (CVP) measurement.

Anesthesia was induced with a sleep dose of thiopental (4–6 mg/kg) as judged by loss of the eyelash reflex, and tracheal intubation was facilitated with pancuronium (0.1 mg/kg). The lungs were ventilated using a Bain anesthetic breathing circuit delivering 66% nitrous oxide in oxygen at a total fresh gas flow of 100 ml/kg (17). Tidal volume was adjusted to 10–12 ml/kg with a respiratory frequency of 12–13 breaths/min. Inhalation anesthetics and narcotics were avoided until completion of study. After tracheal intubation and controlled ventilation, 10–15 minutes were allowed to elapse until a steady hemodynamic state was achieved. Hemodynamic variables were recorded every 1.5–2 minutes and a patient was considered stable if there was <10% change in the three consecutive recordings of heart rate (HR), systolic arterial blood pressure (SAP), diastolic arterial blood pressure (DAP), and CVP over a five-minute period. Patients were then given 3 ml NTG solution (2 mg/3 ml) instilled intranasally, 1.5 ml in each nostril. The NTG solution was prepared by dissolving four crushed tablets of 0.5 mg each in 3 ml of normal saline.

Samples of arterial blood for gas analysis were drawn immediately before administration of NTG. Measurements of IOP (described later), SAP, DAP, HR, and CVP were made just before NTG administration (baseline) and 1, 2, 3, 4, 5, and 10 minutes after NTG administration. Mean arterial blood pressure (MAP) was calculated using the formula: $\text{MAP} = \text{DAP} + \frac{1}{3} (\text{SAP} - \text{DAP})$. Surgery commenced after completion of the study.

Study II

Thirty patients, classified randomly into two equal groups, were studied in a double-blind manner. Criteria for selection of patients and their premedication were as in study I. On arrival in the operating theatre, awake (baseline) measurements of IOP, SAP, DAP, and HR were made after a resting period of 5 minutes. All patients then received 3 ml of either normal saline (group 1) or NTG solution (group 2), 2 mg/3 ml, instilled intranasally 2 minutes before induction of anesthesia. The NTG solution was prepared by an individual not involved in the rest of the study who put NTG solution or saline into 5 ml syringes, taped to prevent recognition of solution on the basis of color, and then instilled it intranasally using an opaque IV cannula.

Anesthesia was induced with sufficient thiopental to obtund eyelash reflex, followed by succinylcholine 1.5 mg/kg. After the onset of apnea, laryngoscopy and tracheal intubation were performed taking not more than 30 seconds. Ventilation of the lungs was carried out as described in study I. Inhalation anesthetics and topical lidocaine sprays were not used during induction sequence.

IOP, SAP, and DAP (by sphygmomanometry), and HR (ECG monitor) were recorded 1) before administration of NTG or saline (baseline), 2) after thiopental, 3) 45 seconds after succinylcholine, i.e., after fasciculations had ceased; and 4) 0.5, 2, and 4 minutes after tracheal intubation. The patients were also monitored for intensity of fasciculations by the simple scoring system of Erkola et al. (18) (grade 0, nil; grade I, barely visible fibrillations; grade II, moderate contractions; grade III, vigorous contractions). Conditions for intubation were based on the criteria used by Eisenberg et al. (19): excellent, easy passage without coughing; good, easy passage with slight coughing; fair, easy passage with more than one cough; poor, difficult passage or/with coughing for more than 10 seconds.

IOP measurements

In both the studies, IOP was measured by an ophthalmologist unaware of the purpose and details of the studies. Measurements were made with a hand-held applanation tonometer (accuracy, $\pm 0.5 \text{ mm Hg}$) with the patient supine and with the operating table horizontal. In each patient, readings were taken in both the eyes after topical administration of three drops of 4% lidocaine. The mean of the two readings was recorded.

Statistical Methods

Normality of observations in each group and the homogeneity of variances between the groups were tested and found valid for application of analysis of variance and the Student-Newman-Keuls multiple range test. Significance of within-group differences in IOP, HR, MAP, and CVP was evaluated by two-way analysis of variance. Between-group differences were evaluated by one-way analysis of variance. In case of significance, Student-Newman-Keuls multiple range test was applied to locate the significant pairs. χ^2 Tests were used to compare intensity of fasciculations and conditions for intubation between the two groups.

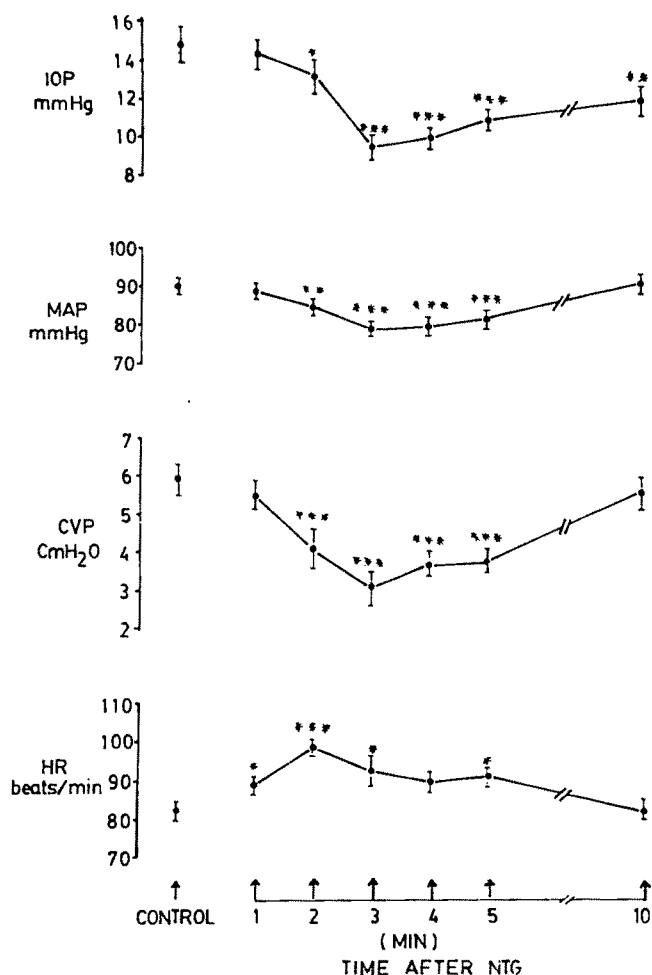


Figure 1. Intraocular pressure (IOP), mean arterial pressure (MAP), central venous pressure (CVP), and heart rate (HR) after nitroglycerin administration in study I. Data are means \pm SEM. * P < 0.05 compared with baseline (control); ** P < 0.01 compared with baseline; *** P < 0.001 compared with baseline.

Results

Study I

There were significant decreases in IOP as well as in MAP and CVP 2, 3, 4, and 5 minutes after NTG administration (Fig. 1). Heart rate increased significantly at 1 minute and remained above the baseline levels for 5 minutes. Ten minutes after NTG administration, the cardiovascular variables returned to the baseline levels while IOP still remained significantly lower. $Paco_2$ ranged from 36 to 39.5 mm Hg (mean 37.3).

Study II

The two groups were comparable in terms of age,

Table 1. Summary of Patient Data (mean \pm SEM) in Study II

	Group 1 (control) (n = 15)	Group 2 (NTG) (n = 15)
Age range (yr)	20-42	20-45
Average age (yr)	28 \pm 1.5	29.4 \pm 1.7
Body weight (kg)	62.8 \pm 4.5	59.4 \pm 2.5
Thiopental (mg)	282 \pm 10.09	270 \pm 8.3
IOP (mm Hg)*	13.86 \pm 0.82	14.73 \pm 0.78
MAP (mm Hg)*	92.4 \pm 2.83	94.06 \pm 2.6
HR (beats/min)*	79.33 \pm 1.61	80.26 \pm 1.74

*Baseline measurements made in the operating theatre before administering pretreatments.

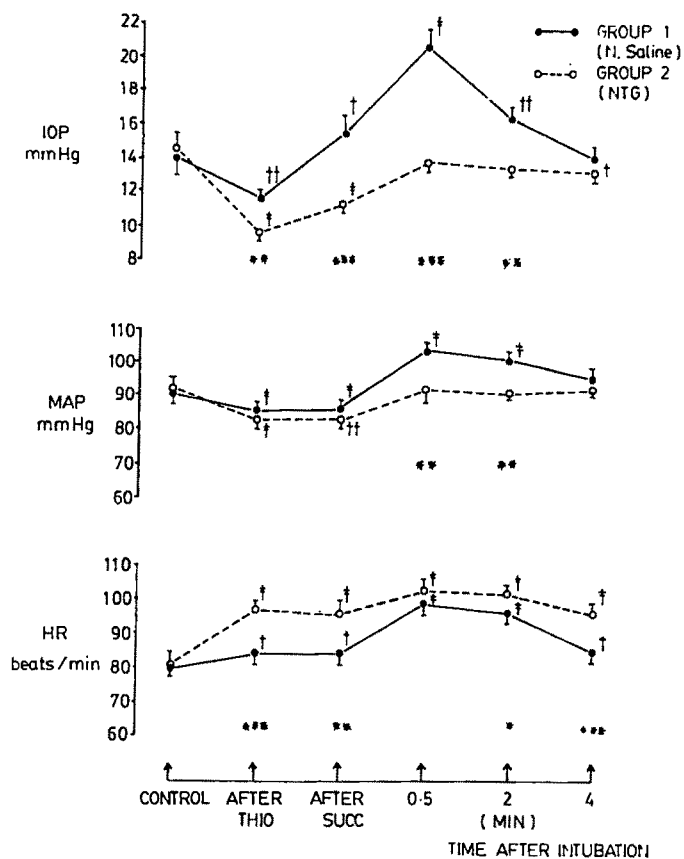


Figure 2. Study II variables at various intervals. Data are means \pm SEM. Abbreviations as in Figure 1. † P < 0.05 compared with baseline (control) within the same group; †† P < 0.01 compared with baseline within the same group; ††† P < 0.001 compared with baseline within the same group; * P < 0.05 between-group comparison; ** P < 0.01 between-group comparison; *** P < 0.001 between-group comparison.

body weight, resting IOP, pulse rate, MAP, and the dose of thiopental (Table 1).

IOP decreased significantly after thiopental in both the groups (Fig. 2). However, in patients pretreated with NTG, this decrease was greater than in patients pretreated with saline (Table 2). In the saline (control)

Table 2. Mean \pm SEM Values and Changes in Intraocular Pressure (IOP) in Study II

	IOP (mm Hg)				Change in IOP			
	Baseline a	After thiopentone b	After succinylcholine c	0-5 min. after intubation d	After succinylcholine		After intubation	
					After thiopentone a-b	From baseline c-a	From post thiopentone value c-b	From post succinylcho- line value d-c
Group 1 (saline)	13.86 \pm 0.82	11.6 \pm 0.56*	15.68 \pm 0.83†	20.9 \pm 0.79‡	2.2 \pm 0.53	1.83 \pm 0.69	4.02 \pm 0.77	7.1 \pm 0.8
Group 2 (NTG)	14.73 \pm 0.78	9.6 \pm 0.45‡	11.3 \pm 0.43‡	13.9 \pm 0.59	5.13 \pm 0.63§	-3.43 \pm 0.82	1.7 \pm 0.39#	-0.83 \pm 0.88

* $P < 0.01$ compared to baseline within same group; † $P < 0.05$ compared to baseline within same group; ‡ $P < 0.001$ compared to baseline within same group; § $P < 0.01$ compared with group 1; || $P < 0.001$ compared with group 1; # $P < 0.05$ compared with group 1.

group, succinylcholine increased IOP significantly above the preinduction levels (Fig. 2). Tracheal intubation increased it further. In NTG group, after succinylcholine, IOP remained significantly below preinduction levels. After tracheal intubation IOP increased and returned to the preinduction level. There was no further increase during the study. When compared with the saline group, changes in IOP after succinylcholine and after tracheal intubation from their preceding values were significantly less in NTG group (Table 2).

Pressor responses to tracheal intubation were blunted in NTG group (Fig. 2). HR values were consistently higher in NTG group than in the control group. None of the patients of either group required any therapeutic intervention for hemodynamic changes. Conditions for intubation were similarly either excellent or good in all patients in both groups. The incidence and intensity of fasciculations were also similar in both the groups ($P > 0.05$).

Discussion

To study the effect of a drug on IOP in anesthetized patients, it is essential that all factors that may influence IOP be controlled. Most anesthetics (1,20), with the exception of ketamine (21), decrease IOP. Succinylcholine, tracheal intubation, patient position, $Paco_2$, surgical stimulation, hemodynamic changes, venous congestion of the head, coughing, and airway obstruction can all affect IOP (1,20). To control for these various factors, in study I we elected to use only $N_2O:O_2$ as the anesthetic after thiopental induction. Also, succinylcholine was avoided and, after tracheal intubation, a steady hemodynamic state was established before administration of NTG. Adequacy of ventilation was confirmed by arterial blood gas analysis. Patients were kept supine and free of surgical stimulation during the study period.

Our results (study I) indicate that intranasal administration of 2 mg NTG causes a significant decrease in IOP in anesthetized patients. In the past Wizeman and Wizeman (16) reported decrease in IOP after IV infusion of NTG in conscious subjects. Our decision to use NTG intranasally followed the results of a study by Hill et al. (22) that found intranasal administration of NTG to be a safe, rapid, convenient, and economical alternative to IV administration. The selection of dose was based on a recent clinical trial (23) in which intranasal administration of 2 mg NTG had been used effectively to control pressor response to laryngoscopy and tracheal intubation in adult patients undergoing coronary artery bypass graft surgery. The patients in study I also had decreases in CVP and arterial blood pressure, which are known to influence IOP (1,20). Although decreases in IOP, MAP, and CVP occurred simultaneously during the initial period of study, 10 minutes after NTG administration, IOP remained significantly lower while hemodynamic variables had returned to the baseline levels (Fig. 1). Similarly, previous workers (16) were unable to correlate the decrease of IOP after IV or oral administration of nitrates with the pattern of systemic blood pressure. It is possible that mechanisms other than hemodynamic changes are also responsible for the observed ocular hypotensive effect of NTG.

In a clinical situation, control of IOP is most relevant during induction of anesthesia in patients with a full stomach to be operated on for penetrating eye injuries. A smooth and quick intubation without increase in IOP is desired (20). Succinylcholine, the relaxant of choice for rapid intubation (2) is, however, considered potentially detrimental in patients with open eye wounds (1,4). Alternatively, use of nondepolarizing neuromuscular relaxants such as pancuronium, atracurium, or vecuronium is advocated (24-28). But damage to the injured eye remains

because of the ocular hypertensive effect of laryngoscopy and tracheal intubation (1,26). Moreover, there is as yet no ultrarapidly acting nondepolarizing neuromuscular relaxant that can substitute for succinylcholine (1,29,30). To shorten the onset of action of nondepolarizing neuromuscular relaxants, the administration of "priming" doses has been suggested (31). However, this may prove to be hazardous in some patients (32,33). Thus there is a continuing search for methods that will allow tracheal intubation to be facilitated by succinylcholine without increasing IOP.

Our data (study II) suggest that nitroglycerin may be a useful agent in modifying IOP changes during induction sequence. When used as a pretreatment, NTG enhances the ocular hypotensive effect of thiopental and minimizes the increases in IOP associated with succinylcholine and tracheal intubation. In the NTG group IOP did not exceed preinduction levels at any time during the study. However, because our study included patients with normal eyes, application of our data to the open eye requires confirmation. Intranasal administration of NTG (0.75–2 mg) has been described as safe in patients undergoing general anesthesia (22,23,34). Our results confirm the same as none of our patients required any treatment to change their hemodynamics.

Our results do not indicate the mechanism by which NTG affects IOP. A number of the actions of NTG are capable of affecting IOP. The ocular hypotensive effect of NTG itself (study I) appears to be an important factor. Succinylcholine is known to cause contraction of orbital smooth muscles, which, in part, contributes to the associated IOP increase (35,36). Because NTG has a relaxing effect on smooth muscles, it is possible that it acts on orbital smooth muscles as well, thereby blunting their response to succinylcholine. However, this needs confirmation.

The correlation between systemic blood pressure and IOP after succinylcholine (Fig. 2) is poor. However, after tracheal intubation there was a significant rise in both IOP as well as MAP in the control group. Because in the NTG group increases in both IOP and MAP after tracheal intubation were blunted, we believe that prevention of pressor responses provided by NTG plays an important role in controlling increases in IOP associated with tracheal intubation.

We were unable to monitor arterial carbon dioxide tension in study II. Changes in P_{aCO_2} were, however, probably unimportant during the short period of this study, especially because patients were ventilated adequately using a Bain circuit (17).

In conclusion, intranasal administration of nitroglycerin during steady-state anesthesia significantly

decreases IOP and, when employed as pretreatment, nitroglycerin significantly attenuates the increases in IOP that follow succinylcholine and tracheal intubation.

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Disposition of Intrapartum Narcotic Analgesics in Monkeys

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GOLUB MS, EISELE JH, KUHNERT BR. Deposition of intrapartum narcotic analgesics in monkeys. *Anesth Analg* 1988;67:637-43.

Maternal-fetal disposition and neonatal respiratory depressant effect of narcotic analgesics were studied by administration of meperidine (2 mg/kg, IV) or alfentanil (IV infusion, 0.1 mg/kg total dose) during labor in rhesus monkeys. Fetal/maternal plasma ratios were lower for alfentanil, the more highly protein-bound drug (fetal/maternal ratio 0.20 at birth versus 0.46 for meperidine). However, elimination of alfentanil was delayed in the neonate. Indeed, plasma concentrations of alfentanil increased during the first 2 postnatal hours, indicating a compartmental shift from tissues to circulation in the

neonate. As regards respiratory depression, six of ten narcotic-treated monkeys had suboptimal (<60 breath/min) respiratory rates at birth. Respiratory rate was negatively correlated with cord vein normeperidine and meperidine levels; the strongest correlation was with normeperidine ($r = -0.84$, $P < 0.01$). Neonatal normeperidine elimination in the postnatal period was prolonged, as has also been observed in humans. These studies serve as a basis for comparing the neonatal neurobehavioral effects of the two analgesics and support the use of the rhesus monkey as an animal model to further understanding of the effects of narcotic analgesics on neonatal respiration.

Key Words: ANESTHESIA—obstetric.
ANALGESICS—fentanyl, meperidine.

To predict the neonatal safety of analgesics given during labor, pharmacokinetic studies need to be conducted during parturition. Distribution and metabolism in both the fetal and maternal units, maternal-fetal transfer, and physiology and pharmacology at the interface between intra- and extrauterine life must be defined. The purpose of this study was to document the disposition of two intrapartum narcotic analgesics (meperidine and alfentanil) as an initial step in comparing their relative neonatal effects.

Studies of the narcotic analgesic meperidine in human parturients have demonstrated several principles of relevance to neonatal effects (1,2). For example, both the interval between administration of the drug and delivery of the infant as well as formation of active metabolites are important determinants of neonatal effects of intrapartum meperidine. Retrospective studies indicate that infants born 2-3 hours after

meperidine administration are at greater risk for neonatal depression than are infants born after a shorter or longer time period (3-5). In addition, it has been suggested that normeperidine, a pharmacologically active metabolite of meperidine, is involved in the neonatal depressant effects (6). The human neonate is known to metabolize meperidine to normeperidine, which has a prolonged elimination half-life in the early postnatal period (7-9).

Protein binding is also increasingly recognized as a factor influencing neonatal effects of narcotics. The highly protein-bound narcotic, alfentanil, has recently been evaluated for use in obstetrics (10,11). Although fetal/maternal ratios were found to be relatively low, free drug concentrations were estimated to be similar in mother and neonate. Effects on the muscle tone in the neonate were noted.

Studies in human parturients are limited by the requirements of pain management and do not permit administration of arbitrary doses of drug at arbitrary time points. For these reasons, animal models are valuable. Although several studies in sheep (12,13) and monkeys (14) have examined the pharmacokinetics of narcotic analgesics in late pregnancy, there are few animal studies with intrapartum drug administration.

Recently, we have developed methods for moni-

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toring vital signs, fetal heart rate, and uterine contractions and administering drugs during labor in the rhesus monkey (15). In the present study we describe disposition and neonatal respiratory effects of intrapartum alfentanil and meperidine.

Methods

Subjects

Rhesus monkeys (*Macaca mulatta*) were selected from the breeding colony at the California Primate Research Center (CPRC) on the basis of reproductive history suitable for uncomplicated vaginal delivery. They ranged in age from 5 to 15 years and in weight from 4.4 to 11.0 kg. Monkeys were time-mated under standardized protocols so that gestation length was known within ± 3 days. Monkeys were assigned to treatment group to balance maternal characteristics (age, weight, and parity) and fetal sex (as determined by ultrasound imaging) as much as possible.

Animal Housing and Care

All dams were under veterinary care throughout pregnancy. They were housed in individual stainless-steel cages (Hazleton Systems, Aberdeen, MD), were fed Ralston Purina Monkey Chow (Ralston-Purina, St. Louis, MO) twice daily, and received water ad libitum via an automatic system. A 12-hour light cycle (lights off 4 PM to 4 AM) was maintained by an automatic timer. Animal care procedures followed the guidelines of the Federal Animal Welfare Act and guidelines of the Institute of Laboratory Animal Resources, National Research Council (16). CPRC is fully accredited by the American Association for Accreditation of Laboratory Animal Care.

Labor and Delivery

Labor was induced with oxytocin at $>90\%$ term when vaginal examination indicated that spontaneous birth was imminent (Bishop score of 6-7). During labor and delivery, animals were restrained in a primate chair to which they were previously adapted. These procedures have been described in detail (15,17). The drugs were scheduled for administration from 2 to 3 hours before delivery. Information on parturition in the rhesus monkey suggests that second-stage labor begins about 90 minutes before de-

livery. In our experience, analgesic treatment delays the progress of labor by about 1 hour. Thus, we began drug administration when the fetal head entered the birth canal (as determined by visual examination) and immediately after amniotomy. For multiple-dose administration, the first dose was given during first-stage labor and the second dose 4 hours later.

Drug Treatments

Intrapartum treatments included

1. Single-dose meperidine (2 mg/kg IV): five monkeys.
2. Single-dose alfentanil (0.1 mg/kg total dose, 50-minute IV infusion): six monkeys.
3. Multiple-dose meperidine (two doses of 2 mg/kg IV 4 hours apart): three monkeys.

In addition, both meperidine (1 and 2 mg/kg) and alfentanil (0.075 and 0.1 mg/kg) were administered IV prepartum to a pregnant dam and meperidine (1 mg/kg IV) was administered postnatally (<20 hours after birth) to three neonates to determine elimination patterns.

Drug Preparation and Delivery

Drugs were administered intravenously through an injection port to an intravenous line (cephalic vein) established before labor. Food and water were not supplied during labor. Plasmalyte with 5% dextrose was administered with mini-infusion (60 drops/ml) at a rate of $50 \text{ ml} \cdot \text{kg}^{-1} \cdot 24 \text{ hr}^{-1}$ with rate controlled by infusion pump.

Meperidine hydrochloride (Demerol) was obtained from Upjohn Co. as an injection solution of 50 mg/ml and administered at a dose of 2 mg/kg. The meperidine was sterilized with an Acrodisc filter and diluted 1:6 with sterile water before injection. The injection was administered over 2 minutes. This dose was selected as providing plasma drug concentrations appropriate for moderate analgesia in humans.

Alfentanil was obtained from the manufacturer (Janssen Pharmaceutica) as a 0.5 mg/ml solution. It was diluted in Plasmalyte to a concentration of 25 $\mu\text{g}/\text{ml}$ for intravenous infusion via a mini-infusion set. To maintain stable plasma drug levels over a 50-minute period, the following infusion schedule was determined: $2.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 30 minutes; $1.25 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for 10 minutes; $0.6 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$

for 12 minutes. Meperidine was administered to neonates via a saphenous catheter in a volume of 1 ml over 2 minutes.

Blood Sampling and Sample Preparation

For drug assay, 2-ml blood samples were drawn in EDTA and transferred to EDTA-borosilicate tubes (Vacutainer) on ice. Samples were centrifuged immediately and plasma frozen at -70°C until assay.

At birth a 2-ml blood sample was obtained from the cord vein and from the cephalic vein of the dam. Subsequent infant samples (6, 12, and 24 hours after birth) were obtained from either an umbilical artery or saphenous vein catheter placed shortly after birth or by venipuncture when necessary. Maternal samples were obtained by venipuncture of the cephalic vein at the same time points.

Drug Assay

Meperidine and normeperidine were extracted from plasma using the method of Mather and Tucker (18) and quantitated by previously established gas chromatography/mass spectrometry (GC/MS) methods (19). The limit of detection was 1 ng/ml plasma for meperidine and 6.25 ng/ml plasma for normeperidine. Duplicate assays differed by 10% or less. Deuterated meperidine and normeperidine were used for internal standards. Standard curves were linear from 1 to 400 ng/ml and from 0.5 to 12.8 $\mu\text{g/ml}$.

Alfentanil was assayed by radioimmunoassay using antibody supplied by the manufacturer (Janssen Pharmaceutica). Samples were diluted to fit standard curve of 0.01 to 8 ng. Duplicate assays deviated $<7\%$.

Plasma Protein Binding

Meperidine (0.5 $\mu\text{g/ml}$) was dialyzed against undiluted plasma at 37°C for 18 hours. The dialysis membrane (Spectra Por 3) had a molecular weight cutoff of approximately 3500. Subsequent to dialysis, the two fractions were analyzed for drug concentration as defined above.

Statistical Analysis

Parametric group comparisons were made with Student's *t*-test, using either unequal or equal variance procedures as appropriate. Correlations were done

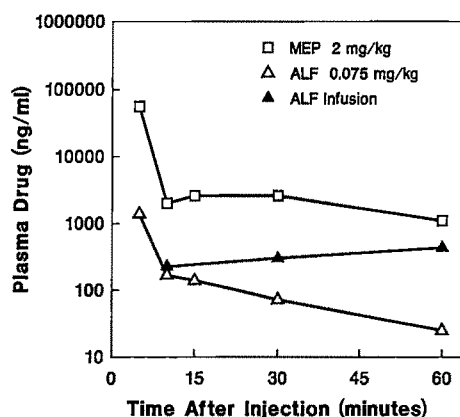


Figure 1. Meperidine and alfentanil plasma levels after administration to a pregnant dam. Abbreviations: MEP, meperidine; ALF, alfentanil.

with the Pearson product-moment correlation. Stepwise multiple regression utilized an entry level significance of 0.15 and was conducted with a general linear models procedure.

Results

Comparison of Meperidine and Alfentanil Distribution in Dam and Fetus

Figure 1 compares plasma drug concentrations in a pregnant monkey after administration of bolus injections of meperidine (2 mg/kg) and alfentanil (75 $\mu\text{g/kg}$). This represents a high analgesic dose of meperidine in humans (20); similar pharmacologic activity was assumed to be reached at alfentanil plasma concentrations about 1/100 of those of meperidine based on the data obtained in humans on relative analgesic potency (21).

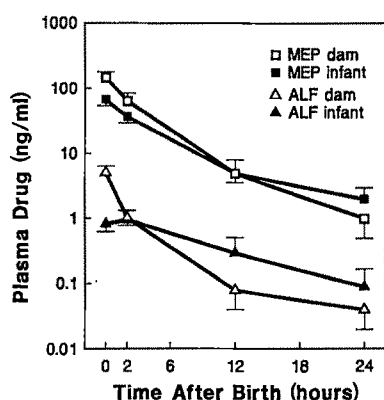
As anticipated, concentrations decreased more rapidly for alfentanil. To simulate an analgesic treatment regimen for intrapartum studies, an infusion rate for alfentanil was derived that maintained stable drug levels over about 1 hour, similar to the duration of action of the bolus meperidine treatment. Plasma levels resulting from the infusion regimen are also shown in Figure 1.

Plasma protein binding, as determined from plasma samples collected from two nonexposed mother-infant pairs at delivery, was 31 and 42% (maternal) and 16 and 15% (fetal) for meperidine.

In Table 1, fetal-maternal ratios of the two narcotics at birth are summarized for five monkeys receiving each drug treatment during labor. Ratios were significantly lower for alfentanil than for meperidine. Disappearance of drug from neonatal and maternal

Table 1. Comparison of Maternal-Fetal Ratios of Meperidine and Alfentanil

	Plasma F/M ratio	
	At birth	2 hrs after birth
Meperidine	0.46 (0.04)*,†	0.51 (0.11)‡
Alfentanil	0.20 (0.14)	0.97 (0.74)

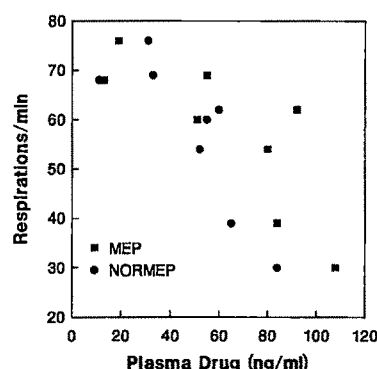
*Mean (SEM), $n = 5/\text{group}$.†Significantly different from alfentanil ratio at birth, $t = 4.95$; $P < 0.01$.‡Significantly different from alfentanil ratio at 2 hrs, $t = 2.73$; $P < 0.05$.**Figure 2.** Disappearance of plasma meperidine (MEP) and alfentanil (ALF) in dam and neonate after intrapartum administration.

plasma after birth is presented in Figure 2. It should be noted that neonatal plasma levels of the two narcotics were within expected pharmacologically active concentrations at birth. After 24 hours, the majority of samples had undetectable drug levels. However, the data clearly demonstrate that there was little or no decline in alfentanil levels in neonatal plasma during the first 2 hours after birth; in fact three of six alfentanil-treated infants had higher plasma drug concentrations at 2 hours than immediately after birth.

Both meperidine and alfentanil were associated with respiratory depression at birth. Six of the ten narcotic-treated monkeys (three meperidine and three alfentanil) had suboptimal (<60 breaths/min) respiratory rates on Apgar tests as compared to none of five control monkeys born under identical protocols (22). Overall Apgar scores were not affected.

Meperidine, Normeperidine, and Respiratory Depression

Figure 3 demonstrates that respiratory rate at birth was highly correlated with neonatal plasma levels of both meperidine ($r = -0.81$, $P < 0.02$) and normeperidine ($r = -0.84$, $P < 0.01$). This analysis includes,

**Figure 3.** Correlation between neonate respiratory rate and cord meperidine (MEP) and normeperidine (NORMEP) levels at birth.

in addition to five monkeys receiving a single meperidine injection, three additional monkeys given two injections spaced 4 hours apart. Because drug effects seemed specific to respiration, absolute respiratory rate was analyzed. Stepwise multiple-regression analysis indicated that plasma normeperidine was a better predictor of respiratory rate than plasma meperidine, the interval between drug injection and delivery, duration of labor length, or combined levels of drug and metabolite. Normeperidine predicted 72% ($P < 0.01$) of the variability in respiratory rate and addition of meperidine and labor length to the regression increased predictability by $<1\%$.

There was a strong negative correlation between drug delivery interval and neonatal plasma concentrations of both meperidine and normeperidine (Table 2). Normeperidine/meperidine ratios were greater in neonate than in dam at the time of delivery, suggesting relatively slower elimination of normeperidine in the fetus than in the dam before birth. After birth, very slow elimination of normeperidine was seen during the first 24 hours in the monkey neonate (Fig. 4A). Although most plasma meperidine levels were below detection limits 12 hours after delivery, normeperidine was still present at appreciable levels at 24 hours.

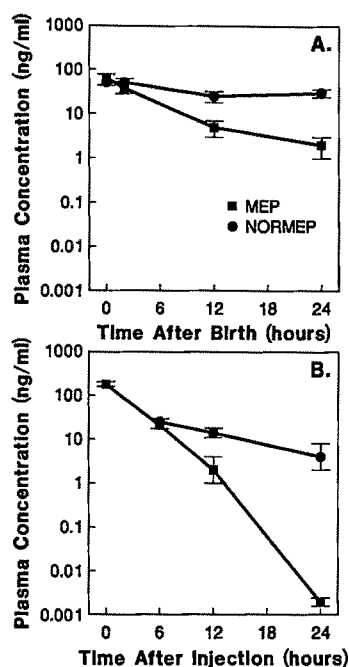
Evidence that the neonate can metabolize meperidine to normeperidine and that neonatal elimination of normeperidine is slow was provided by experiments in which drug was injected directly into two newborn infants. As shown in Figure 4B, normeperidine levels exceeded those of meperidine by 6 hours after injection and remained detectable for as long as 24 hours after the injection.

Discussion

Low fetal/maternal plasma ratios at birth are often taken to indicate relatively low fetal exposure to

Table 2. Comparison of Maternal and Fetal Plasma Levels of Meperidine and Normeperidine at Birth

	Plasma drug (ng/ml)		Correlation with drug-delivery interval	
	Maternal	Fetal	Maternal	Fetal
Meperidine	139 (70)*	63 (24)†	-0.83 [§]	-0.85 [§]
Normeperidine	72 (34)	49 (22)	-0.79	-0.89 [§]
Normep/mep	0.46 (0.06)	0.73 (0.10)‡	0.17	0.16

*Mean (SEM), $n = 8/\text{group}$.†Significantly different from maternal value, $t = 2.83$; $P < 0.05$.‡Significantly different from maternal ratio, $t = 2.55$; $P < 0.05$.[§]Correlation significant, $P < 0.01$.^{||}Correlation significant, $P < 0.02$.**Figure 4.** Neonatal plasma disappearance of meperidine (MEP) and normeperidine (NORMEP) after intrapartum (4A) or postpartum (4B) administration. Intrapartum treatments were given intravenously to the dam about 2 hours before delivery. Postpartum treatments were given intravenously to the neonate about 12 hours after delivery.

drugs administered in the intrapartum period. In the present experiment, fetal/maternal ratios for alfentanil, a highly (>90%) protein-bound narcotic analgesic, were lower than they were for meperidine, which is less (50%) protein bound. However, there are several factors that can lead to high fetal exposures and low fetal/maternal ratios. For example, rapid fetal tissue uptake has recently been suggested as a factor influencing low fetal/maternal ratios of intrapartum bupivacaine (23). Also, low fetal protein-binding capacity led to a fetal-to-maternal concentration gradient of free drug in the presence of low fetal/maternal whole blood ratios after bupivacaine infusion in pregnant sheep (24).

Both these factors, rapid fetal tissue uptake and low fetal protein-binding capacity, may have led to a relatively high fetal-neonatal exposure to alfentanil in the present experiment. The increase in neonatal plasma alfentanil levels in the first 2 hours after birth could represent a compartmental shift from tissues to systemic circulation driven by relatively high tissue levels of alfentanil due to rapid tissue uptake. Also, alfentanil protein binding in humans has been demonstrated to be lower in the neonate than in the mother, leading to approximately equivalent free drug levels (10). Thus, the relatively lower fetal/maternal ratios at birth for alfentanil as compared to meperidine cannot be interpreted as reflecting less exposure to intrapartum drug and less likelihood of neonatal effects.

As regards meperidine-induced respiratory depression, regression analysis suggests that plasma normeperidine concentrations were more closely associated with respiratory depression than were meperidine concentrations. However, the limited number of subjects prevent confirmation of this association. Studies in humans suggest an involvement of normeperidine (6), but have failed to find a correlation between cord vein drug levels and depression in the neonate. However, the majority of these studies in humans used the Apgar as the only measure of depression. We found that depression was specific to the Apgar scale measuring respiratory rate; heart rate, muscle tone, and responsiveness were not depressed in the drug-treated infants. As suggested previously, a more quantitative and specific measure than the Apgar may be needed to define the correlation between drug concentrations and respiratory depression at birth in humans (25,26).

There is considerable difficulty comparing these data to studies in human parturients; each clinical study is based on a unique combination of drugs, drug doses, number of administrations, routes of administration, and analytical techniques. Also all human studies will be subject to the constraints of

pain management. Nonetheless, in general it can be said that neonatal meperidine plasma levels were equivalent to those seen in human infants at similar maternal doses. However, fetal/maternal ratios (cord vein to maternal vein) were lower (0.46) than usually reported in humans (0.76–0.82). This suggests either 1) less maternal–fetal transfer in monkeys than in humans or, 2) a more rapid tissue uptake and/or metabolism by the monkey fetus. As the normeperidine/meperidine ratios in monkeys were also considerably higher than in humans, greater uptake and metabolism are suggested. More rapid metabolism would also explain the negative correlation between normeperidine and drug delivery interval; a positive correlation (accumulation of normeperidine) is typically reported in human experiments (5,27), although there is limited information for the 2- to 4-hour intervals studied here. Fetal and neonatal metabolism of meperidine to normeperidine in rhesus monkeys are demonstrated by our experiments, in contrast to those of Morrison et al. (28). As regards alfentanil, fetal/maternal ratios in monkeys (0.20) are similar to those reported with human obstetric use (0.14–0.31) (10,11,29).

These experiments demonstrate that intrapartum drug disposition can be studied under closely defined protocols and with relatively small numbers of monkeys. Intrapartum pharmacokinetics have not been sufficiently characterized in either human or nonhuman primates to permit an evaluation of the adequacy of the monkey as a model for the human. However, many factors, such as placental structure, maturity at term, single offspring pregnancy, and physiology of labor (15,20), are so similar as to encourage confidence in generalizability from monkey studies to human clinical situations.

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A Random Survey of Anesthesia Machines and Ancillary Monitors in 45 Hospitals

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KUMAR V, HINTZE MS, JACOB AM. A random survey of anesthesia machines and ancillary monitors in 45 hospitals. *Anesth Analg* 1988;67:644-9.

One hundred sixty-nine anesthesia machines and ancillary monitors were tested in 45 hospitals, randomly selected to assure a sample of hospitals with a wide range of anesthesia workload. The machines ranged in age from 1 to 28 years (8 ± 6 , mean \pm SD), with 47.3% manufactured since 1980, 39.1% between 1970 and 1980; and 13.6% before 1970. Regular maintenance was provided for 112 machines (66.2%) by the manufacturer, whereas 55 machines (32.5%) were maintained by independent contractors. Two machines designated as backup machines received no maintenance. There was no source of oxygen to back up oxygen piped from a central source on five machines. Thirteen machines had leaks over 500 ml/min distal to the common gas outlet, the most common sites being the carbon dioxide absorber, dome valves, and oxygen monitor sensor adaptors. Another two machines had leaks over 500 ml/min proximal to the common gas outlet. Forty-two of the 169

machines did not have an oxygen analyzer; another 18 had oxygen analyzers that did not function properly. Only 29 (23.5%) of 123 machines equipped with a ventilator had a working high-pressure alarm, whereas functioning low-pressure alarms were available on 104 machines (84.5%). Fourteen of the 383 vaporizers tested for calibration did not meet the calibration standard recommended by the manufacturers. None of the 32 liquid anesthetic samples collected and analyzed during the survey showed contaminants. Only four (8.8%) hospitals utilized a written anesthesia machine checklist. There was no correlation between the number of malfunctions observed and ages of the machines, although the older machines tended to lack the basic monitoring devices and safety features. Equipment inadequacies encountered during the survey period ranged in degree of severity. All such inadequacies were pointed out to the facilities involved. Those inadequacies considered to be major in nature have been rectified.

Key Words: EQUIPMENT, ANESTHESIA MACHINES—safety.

Although critical incidents or anesthesia mishaps due to equipment failure are uncommon, they occur sufficiently often to be of major concern to anesthesiologists (1-3). A retrospective survey of critical incidents by Cooper et al. (2) identified equipment failure as the second most common cause of preventable mishaps in anesthesia practice. Equipment-related incidents may result directly from equipment malfunctions or indirectly from user error.

Because of capital spending limitations, the equipment inventories of many hospitals include anesthesia machines that vary greatly in age. During the past 50 years, anesthesia machines have undergone revo-

lutionary changes. New technology, monitoring devices, and machine design have probably contributed significantly toward the development of safer anesthesia machines. Although we acknowledge that safety features of current technology may have enhanced human vigilance and therefore reduced anesthesia risks, little attention has been given to assessing existing mechanical performance and safety features of older equipment still in active use. The present survey was conducted under a contract between the U.S. Food and Drug Administration and the Iowa Department of Public Health in collaboration with the Department of Anesthesia, University of Iowa College of Medicine, to evaluate mechanical performance of anesthesia gas delivery systems (AGDS) and ancillary monitors in the state of Iowa.

Methods

All hospitals in the state of Iowa were first listed and

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Table 1. Distribution of AGDS by Bed Capacity of Hospitals and Year Manufactured

Hospitals participating		Machines manufactured		
Bed capacity	No. hospitals	Before 1970	1970-79	1980-present
≥200 beds	9	7	30	56
50-200 beds	13	7	21	13
≤50 beds	23	9	15	11

classified into three groups according to bed capacity. Forty-five hospitals were selected at random from the three groups to assure a proportionate sample of hospitals with wide range of workload. Twenty-three of the hospitals surveyed had less than 50 beds, 13 had between 50 and 200 beds, and 9 had more than 200 beds (Table 1).

The cooperation and support of several professional organizations were essential to the conduct of the project. To accomplish the goals of the contract, the Iowa Hospital Association (IHA), Iowa Society of Anesthesiologists (ISA), and the Iowa Association of Nurse Anesthetists (IANA) were very helpful in providing such support and achieving the voluntary participation of the selected hospitals. Voluntary participation was sought from the hospitals by assuring them anonymity with respect to data obtained during the study and included in the final report, as well as by providing each hospital with detailed individual reports. Only one hospital expressed concern regarding the release of information it considered proprietary. Although the Iowa Public Health Department could have mandated this inspection, it was decided to keep this study entirely voluntary. This one hospital was therefore replaced with another facility from an alternative list.

Coordinating the schedule of hospital visits consisted of forwarding an appropriate letter describing the purpose of our survey to both the hospital administrator and the chief of anesthesia. The letter emphasized four major points:

1. The earlier-mentioned professional associations supported the project.
2. The individual hospital survey results would not be identifiable as to individual hospitals in any way, either during the study or in the final report.
3. We wished to arrange a time for the survey at the convenience of the hospital and would like to have someone knowledgeable in AGDS present during the survey.
4. An interview would be conducted on completion of our survey, a copy of all test results would be provided to each hospital, and a copy of our final report would be sent on FDA approval.

Before the sample hospitals were contacted, the protocol was tested at the University of Iowa Hospital. This enabled us to standardize our procedures and gain valuable experience in conducting the survey. Data from a test of equipment at the University of Iowa Hospitals were not included in the final report.

The survey consisted of a questionnaire and on-site inspection of the AGDS. The questionnaire was sent to the chief of anesthesia as an attachment to the letter confirming participation in the survey. The questionnaire sought information about the number of AGDS, number of years in use, maintenance history, modifications performed on machines since purchase, number of anesthetics per year using the AGDS, and number of people using them. The questionnaire was returned during the on-site inspections. The inspections of the anesthesia systems were completed according to guidelines prepared by us from recommended standards by various regulatory agencies and manufacturers (4). Approval of these guidelines was obtained before the inspection from the Federal Center for Devices and Radiological Health. The on-site inspection of AGDS included checking of piped and cylinder gases for pressure, inspection and measurement of accuracy of flow meters, placement and calibration of vaporizers (Riken portable gas analyzer); and examination of the functioning of ventilators and their alarms. All AGDS were tested for any gas leakage. Various tests were performed to localize whether the leakage was proximal to common gas outlets or in the breathing system. The leaks were quantitated by recording the flow of oxygen (ml/min) needed to maintain a pressure of 30 cm H₂O at the common gas outlet or in the breathing system. Leakage at yokes were tested separately by observing the decrease in pressure at the cylinder pressure gauges after cylinder pressure had been checked and the valve closed (5). Each AGDS was also inspected for presence and proper functioning of an oxygen analyzer, ventilator rate and pressure alarm, oxygen/nitrous flow ratio alarm, and oxygen pressure "fail-safe" mechanism. Liquid anesthetic samples were collected from vaporizers that were inaccurate (i.e., ±25% calibration error) and, during the latter part of the survey, one additional random sample of vaporizer contents was taken from each facility. A total of 32 liquid samples were analyzed for contaminants using gas chromatography interfaced to a mass spectrometer. A Riken portable gas analyzer was used to measure the accuracy of vaporizers at a flow rate of 4 L/min for precalibrated vaporizers and 3 or 5 L/min for Copper Kettle and Vernitrol vaporizers. Upon completion of the survey,

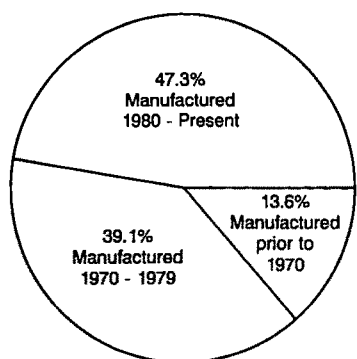


Figure 1. Distribution of AGDS by age.

a written report of the inspection of each AGDS was given to the hospitals. A copy of the final report was sent to each hospital at the conclusion of the study.

Results

One hundred sixty-nine anesthesia machines were tested according to the above protocol at 45 hospitals. These hospitals performed 67,243 procedures using these machines during 1985, 61.7% of these procedures being performed by anesthesiologists, and the remaining 38.3% by certified registered nurse anesthetists (CRNAs).

The machines ranged in age from 1 to 28 years, with 47.3% manufactured since 1980, 39.1% between 1970 and 1979, and the remaining 13.6% before 1970 (Fig. 1). The oldest machine in operation was manufactured in 1958. More than half (52.1%) of the machines used at survey sites were manufactured by Ohio/Ohmeda. The remaining machines in use included 33.1% manufactured by Foregger, 13.6% by North American Dräger, and 1.2% by Fraser-Harlake (Fig. 2). Twenty-six of the 169 anesthesia machines (located in 20 of the 45 hospitals) were designated as "backup" machines, but 15 of these backup machines were said to be "never" actually used.

Routine maintenance and servicing four times a year was provided for 112 machines by the manufacturer, whereas 55 were serviced by independent contractors, including one hospital employee who performed this service at his facility. Two of the 15 unused backup machines received no maintenance.

Twenty-four hospitals had no reporting system for critical incidents, whereas the remaining 21 facilities reported equipment related incidents to manufacturers, within the facility, to regulatory agencies or to the United States Pharmacopeia's problem reporting system (U.S.PPRS).

Of the 169 machines tested, 56 had undergone some modification since delivery from the manufac-

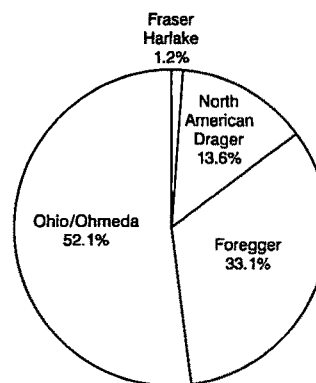


Figure 2. Distribution of AGDS by manufacturer.

Table 2. Summary of Monitors and Alarms

Device	Percentage of machines with device	Percentage working
Oxygen monitor	75.1	85.8
Ventilator rate monitor*	19.5	83.3
Ventilator low-pressure alarm*	87.0	92.2
Ventilator high-pressure alarm*	27.2	93.5
Oxygen/nitrous flow ratio alarm	18.9	100
Oxygen pressure fail-safe	100	100

*Percentage based on 123 machines equipped with a ventilator.

turer. Most (93%) of these modifications were performed either by the manufacturer or maintenance providers. These modifications consisted primarily of addition of vaporizers, ventilators, scavenging systems, monitors, and alarms. Modifications of the remaining four machines (7%) were performed by in-house personnel. One modification encountered involved the compromise of a double vaporizer lock-out mechanism, although an internal system disallowed the possible delivery of two anesthetics at the same time.

Five machines in this survey had no source of oxygen to back up oxygen piped from a central source, whereas all remaining machines had E-size cylinders as backup sources. Forty-six of two hundred sixty-eight oxygen cylinders tested had pressure less than 600 psi (6).

Forty-two (24.8%) of the machines did not have an oxygen analyzer. Eighteen (14.1%) of the monitors used did not function properly either due to worn out sensors or low batteries (Table 2). Thus, 60 machines (35.5%) were not equipped with functioning oxygen analyzers.

O₂/N₂O flow ratio alarms were present in 32 machines. All worked satisfactorily. All machines had functioning O₂ pressure fail-safe mechanisms.

Fifteen machines had a leak of more than 500 ml/min. Out of these 15 machines with leaks, only 2

Table 3. Summary of Vaporizers Tested

	No. encountered	No. tested	No. inaccurate
Precalibrated	337	334	10
Copper Kettle	33	21	2
Vernitrol	41	28	2
Total	411	383	14

machines had leaks proximal to the common gas outlet, whereas the remaining 13 had a leak distal to the common gas outlet (i.e., in breathing system), the most common site being carbon dioxide absorber, dome valve, and oxygen monitor sensor adaptor. Thirty-three machines (19.5%) of the 169 tested had at least one yoke block that did not pass the high-pressure test, indicating a defective or leaky yoke block check valve.

A total of 411 vaporizers were surveyed, 28 of which were said to not be in clinical service at the time of our visits. The remaining 383 vaporizers were tested for calibration (Riken portable gas analyzer, model 18). Fourteen vaporizers did not meet calibration standards recommended by their manufacturers (Table 3). Twenty vaporizers had been added downstream of the machines' common gas outlets. In 29.6% of the machines, the pin indexing safety feature for filling the vaporizers was available for at least one of the vaporizers. In 39 facilities vaporizers were filled by anesthesia providers; at the 6 remaining facilities they were filled by other operating room personnel. None of the 32 liquid anesthetics collected at random during this survey showed any contaminants when analyzed using gas chromatography interfaced to a mass spectrometer.

One hundred twenty-three machines were equipped with a ventilator, 73 (59.3%) utilizing a hanging bellows, and 50 (40.7%) utilizing a rising (standing) bellows. Only 24 of the 123 anesthesia machines equipped with ventilator had ventilator tidal volume and rate monitors and 4 of these monitors did not function properly. There was no low airway pressure alarm on 16 ventilators and another 3 were inoperable. High-pressure alarms were available on 31 machines (25.2%), 2 of which did not function properly.

Only 95.5% machines in this survey were equipped with a scavenging system. The scavenging system connectors and the breathing circuit connectors were indistinguishable on 24.3% of the machines surveyed.

All electrically equipped machines checked in this survey for chassis leakage were within the maximum limit of 100 microamperes as recommended by the

Association for Advancement of Medical Instruments (7).

Discussion

In the United States, general anesthesia is administered about 20 million times each year and has been said to be the primary cause of death of at least 2000 patients (8). Most investigators interested in this problem have concluded that at least half of these deaths are preventable (8-13). Inadequate supply of oxygen to the brain and other vital organs is one of the commonest causes of anesthesia-related injuries or deaths. In 21 incidents investigated by Spooner et al. (14) an oxygen analyzer was not in use in 15 of the incidents and proper functioning of one analyzer was questioned in another case. All 21 of these patients had hypoxic episodes. It is considered likely that some of these adverse outcomes could have been avoided if functioning oxygen analyzers were in use. Despite this, in our study we were surprised to find that 42 of the 169 machines (25%) surveyed did not have an oxygen analyzer at all, and another 18 analyzers did not function properly. Their improper function was not a minor calibration error. They would not have warned of delivery of hypoxic gas mixture. In a similar survey conducted by the Texas Department of Health, 19 of 65 machines (29%) had no oxygen analyzer, whereas another 4 did not function properly because of low batteries (15). Airway disconnect alarms, perhaps an even more important monitoring device, were missing or nonfunctioning on 19 of the 123 AGDS with a ventilator in our survey. Of the 46 machines without ventilators, none had any mechanical or electrical airway disconnect alarm at all. If used properly, airway disconnect alarms and oxygen analyzers can help detect serious errors before serious or permanent damage occurs. Numerous authorities believe that there is no reason not to have such basic monitoring devices for each AGDS no matter when manufactured. To achieve full benefits of these devices they must be calibrated before each use and must receive regular maintenance. Our finding that 18 of the oxygen analyzers and three of the airway disconnect alarms that were present but did not function is thus distressing.

Many of the equipment-related anesthesia mishaps can be traced specifically to preinduction conditions, a majority of which can be prevented by preuse inspection of the equipment. Despite this, only 3 of the 45 hospitals visited in our survey had any kind of written preanesthesia equipment checklist. Emergency Care Research Institute, FDA, and ASA have

urged anesthesia providers to routinely use an equipment checklist (6,16). A modified version of such a checklist was used in a prospective study previously reported (17), which might have been one of the contributory factors in reducing the incidence of preventable mishaps.

Regular preventive maintenance and use of a preuse inspection checklist could have helped in detecting 18 nonfunctioning O₂ analyzers, three ventilator disconnect alarms, 15 machine leaks of over 500 ml/min, inadequate gas line supply pressure at two facilities, and lack of source of oxygen to back up oxygen piped from a central source on 5 machines in our survey. Anesthesia machines should receive regular maintenance at least twice a year, whereas other equipment, including oxygen analyzers, capnographs, airway disconnect alarms, and so on, may benefit from more frequent inspection and service (18). The majority of the AGDS in our survey received preventive maintenance from the manufacturers, but some facilities had maintenance contracts with independent contractors. The long-term implications of maintenance provided by independent contractors whose work is not checked are yet to be determined. No literature exists on the subject one way or the other.

Anesthesia mishaps due to equipment failure, although few in number, present considerable risk of human suffering, liability costs, and loss of credibility of the medical profession. It is important for clinicians to understand the capabilities, limitations, and operation of each AGDS they use. Antiquated equipment for which it is difficult to obtain parts or regular preventive maintenance should be replaced. Obsolete equipment without airway disconnect alarms is a major concern to us. The costs of new equipment are major factors, but questions of liability arising from using obsolete equipment should be kept in mind.

The growth of technology in anesthesia, which has been astonishing over the past several years, continues to change. Continuing education addressing the basic mechanics of the AGDS and the new advances in the field is essential for the safe and effective delivery of anesthesia. Although specific data are difficult to obtain, it is evident from our survey that most clinicians spent little time during their training learning about AGDS. It also appears that few AGDS users are aware of the various avenues available to them for reporting malfunctions and adverse incidents.

Although numerous machine inadequacies were determined from our survey, those that posed a significant health problem were followed up until corrected. There was no correlation between the age

of AGDS and the number of malfunctions observed. The mechanical performance of the majority of older AGDS was satisfactory, although safety features and essential basic monitoring devices (e.g., O₂ analyzers, and airway disconnect alarms) were not often present. The delivery of hypoxic gas mixtures or disconnections might be expected to be more difficult to detect when older AGDS without basic safety features and monitoring devices are used.

Some of the suggestions for modifications in AGDS offered by AGDS users in the course of our survey included

1. Standardization of the locations of anesthetic-specific vaporizers.
2. Standardize and distinguish the tones of various alarms to avoid confusion when using different makes and models of equipment.
3. Incorporate more monitors as standard equipment on AGDS, especially pulse oximeters and capnographs.
4. Provide a larger work space on the machine.
5. Require certification of preventive maintenance providers to ensure quality control.

In conclusion, it is evident from our survey that numerous anesthesia machines employing very few modern safety features are still in active use. Even the most basic of monitoring devices were absent on these AGDS. All the significant equipment inadequacies encountered during the survey were pointed out to the specific hospitals. Most of these inadequacies have been corrected. Proper regular maintenance, update or replacement of equipment as needed, use of appropriate monitoring devices, and a preuse equipment checklist may help in improving the quality of patient care and decreasing the morbidity and mortality associated with anesthesia equipment. We also believe that it is within the province of state departments of health to encourage and/or conduct similar regular inspections of such life-supporting equipment.

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Atropine-Edrophonium Mixture: A Dose-Response Study

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Atropine-edrophonium mixture: a dose-response study.
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The dose-response and the doses required to prevent bradycardia in 50% (ED₅₀) and 95% (ED₉₅) of patients were determined for atropine after antagonism of pancuronium-induced neuromuscular blockade in 72 patients with edrophonium-atropine mixtures. Edrophonium 0.67 mg/kg (group A, n = 37) or 1.0 mg/kg (group B, n = 35) was randomly mixed with one of seven doses of atropine (ranging from 0.0125 to 0.0215 mg/kg in group A and from 0.02 to 0.04 mg/kg in group B); with dose-response curves for atropine being constructed for both groups 5 and 10 minutes after the injection of the mixture. These dose-re-

sponse curves were found to be parallel in both groups. The calculated ED₅₀ values of atropine were 1.6-2 times greater in group B, compared with those in group A. The estimated ED₅₀ doses of atropine in groups A and B at 5 minutes were 0.018 and 0.029 mg/kg, respectively, and at 10 minutes, the ED₅₀ doses were similar, being 0.016 and 0.032 mg/kg, respectively. The calculated ED₉₅ doses of atropine in groups A and B at 5 minutes were 0.024 and 0.055 mg/kg, and at 10 minutes, the ED₉₅ doses were also similar, being 0.027 and 0.05 mg/kg, respectively.

Key Words: ANTAGONIST, NEUROMUSCULAR RELAXANTS—edrophonium. HEART—pulse rate. PARASYMPATHETIC NERVOUS SYSTEM, PHARMACOLOGY—atropine.

Edrophonium can, in adequate doses, produce a rapid onset of antagonism of nondepolarizing muscle relaxants with a duration of action equivalent to that of neostigmine (1-4). Rupp et al. (5) suggested that the edrophonium dose should be at least 1 mg/kg to achieve antagonism as rapid as that seen with neostigmine 0.04 mg/kg when twitch height is 2-10% of control levels.

Atropine or other anticholinergic drugs must be given to prevent bradycardia associated with use of anticholinesterases. However, the dose of atropine required to prevent bradycardia during antagonism of neuromuscular blockade with higher doses of edrophonium (>0.5 mg/kg) has not been evaluated in adults. Further, the dose-response relation has not been studied for atropine after simultaneous administration of atropine and edrophonium.

Therefore, we compared the atropine require-

ments of two doses of edrophonium (0.67 and 1 mg/kg) in terms of changes in heart rate and evaluated the dose-effect relation for atropine at various intervals. We also estimated the dose of atropine required to prevent bradycardia in 50 and 95% of the patients, i.e., ED₅₀ and ED₉₅, respectively, with the two doses of edrophonium.

Methods

After institutional approval, 72 ASA physical status I or II patients undergoing elective surgical procedures were studied. All patients were free of cardiac, neuromuscular, renal, and hepatic disease. All had normal preoperative ECGs and normal laboratory values for serum electrolytes, BUN, creatinine, SGOT, and alkaline phosphatase. Informed consent was obtained. All patients were premedicated with diazepam 10-15 mg orally 90 minutes preoperatively.

An intravenous infusion of lactated Ringer's solution in 5% dextrose was started before induction of anesthesia. The ECG (lead II) and nasopharyngeal temperature were monitored continuously. Blood

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Table 1. Atropine Dose, Control Heart Rate, and Heart Rate after Antagonism of Pancuronium-Induced Neuromuscular Blockade in Group A with a Mixture of Edrophonium 0.67 mg/kg and Different Doses of Atropine

Group A (n = 37)	Atropine Dose (mg/kg)	Heart rate (beats/min)														
		Control	After reversal (minutes)													
			1	2	3	4	5	6	7	8	9	10	15	20	25	30
A-1 (n = 7)	0.0125	83.1 (4.1)*	85.1 (4.7)	76.8 (4.5)	73.2† (4.5)	71.5† (4.8)	71.0† (4.9)	71.0† (4.8)	72.1† (4.6)	71.7† (5.2)	71.8† (5.3)	72.5† (5.8)	88.7 (5.9)	85.4 (5.7)	84.2 (4.9)	85.1 (8.3)
A-2 (n = 5)	0.014	83.4 (6.9)	78.0 (7.6)	73.4 (4.8)	73.8 (5)	73.6 (5.7)	73.2 (5.4)	73.8 (5.3)	72.8 (5)	73.8 (4.7)	75 (4.6)	75.8 (5)	74.4 (4.4)	79.8 (6.2)	86.0 (7.2)	86.8 (7)
A-3 (n = 5)	0.0155	78.4 (4)	73.6 (10.8)	67.6† (6.6)	64.8† (5.8)	66.0† (6.9)	62.8† (4.1)	63.2† (3.7)	64.0† (3.9)	64.2† (4.3)	63.8† (3.9)	64.2† (3.8)	77.6 (4)	78.6 (8.1)	85.8 (8.4)	87.8 (11.6)
A-4 (n = 5)	0.017	77.0 (6.7)	87.2 (5.4)	83.2 (6.4)	77.2 (4.6)	75.8 (4.1)	75.6 (4.3)	76.2 (3.8)	76.0 (4.1)	75.4 (4.4)	74.4 (4.1)	75.0 (4.1)	76.6 (5.7)	79.4 (4.2)	89.2† (7.6)	92.8 (4.6)
A-5 (n = 5)	0.0185	81.4 (4.6)	100.6† (4.9)	84.4 (6)	81.6 (4.8)	81.8 (4)	83.2 (4.5)	81.6 (3.3)	82.8 (3.4)	83.0 (3.9)	85.0 (3.2)	86.4 (2.2)	85.4 (4.5)	96.0 (3.3)	96.0† (1.4)	103.6† (6.8)
A-6 (n = 5)	0.020	93.6 (3.3)	111.4 (8.3)	103.2 (6.8)	99.8 (5)	98.0 (5.2)	97.6 (4.7)	96.4 (4.9)	94.6 (4.6)	93.8 (4.6)	92.2 (4.7)	90.8 (4.4)	87.6 (3.1)	94.8 (4.1)	105.2† (2.4)	101.0 (5.2)
A-7 (n = 5)	0.0215	85.2 (5.8)	104.8† (6.2)	92.6 (7)	87.8 (8.1)	88.4 (8.6)	89.2 (9)	89.6 (8.6)	88.8 (8.7)	88.8 (8.2)	90.4 (8.4)	90.2 (8.7)	86.0 (6.4)	92.0 (5.7)	104.8† (5.5)	101.2 (8.5)

*Mean values (\pm SEM) are shown.†Different from control ($P < 0.05$).

pressure was measured by an electronic oscillotonometer (Dinamap). In all patients, anesthesia was induced with fentanyl 2 μ g/kg and thiopental 5 mg/kg and was maintained with 70% nitrous oxide in oxygen and halothane (0.5–1% inspired). Pancuronium 0.1 mg/kg was administered to provide neuromuscular blockade. Ventilation was adjusted to maintain normocapnia and end-tidal CO₂ was monitored using a Datex infrared CO₂ analyzer.

Neuromuscular activity was assessed by observation of thumb adduction, using a Bard peripheral nerve stimulator applying supramaximal stimuli to the ulnar nerve at the wrist. Observation of thumb adduction was made easier by fixing the medial four fingers with adhesive tape to an armboard and the arm abducted to approximately 90°. Train-of-four (TOF) stimuli was used throughout the study. At the conclusion of surgery, patients were assigned randomly to one of two groups (group A, $n = 37$, and group B, $n = 35$). When recovery of two of the four responses in the TOF occurred, the neuromuscular blockade was antagonized with edrophonium 0.67 mg/kg and 1.0 mg/kg in groups A and B, respectively. Edrophonium was randomly mixed with one of the seven doses of atropine in each group as shown in Tables 1 and 2. Five patients were studied at each dose of atropine except for seven patients in subgroup A-1. The edrophonium-atropine mixture was administered as a single bolus injection. Control heart rate was the rate immediately before the administration of the drug mixture. Heart rate (as measured by ECG) was recorded at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, and 30 minutes after antagonist administra-

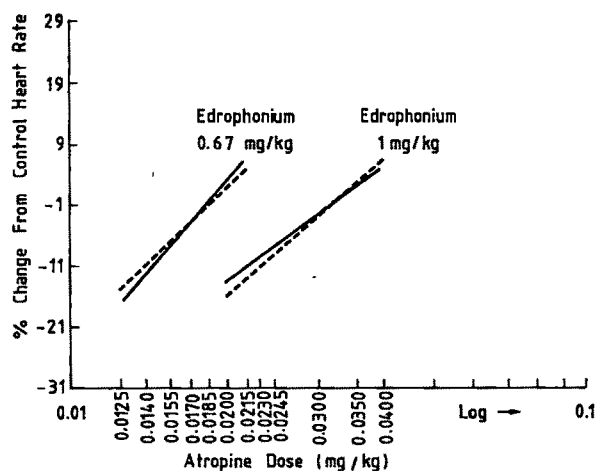
tion. Patients continued to inhale nitrous oxide in oxygen and 0.5–1% halothane for 10 minutes after the administration of the antagonist. Patient stimulation was avoided during this period. After the measurements at the 10th minute, nitrous oxide and halothane was discontinued and 100% oxygen was given. With the return of all responses of TOF stimulation and the presence of a sustained muscle contraction in response to a tetanic stimulus (50 Hz for 5 seconds), the tracheal tube was removed. Further assessment of patients was carried out in the recovery room for 60 minutes, using clinical criteria such as ability to open eyes, cough, and sustain a head lift. The ECGs were examined in detail for changes in heart rate and rhythm.

Data Processing

Statistical analyses were performed by the BMDP (1987) statistical package. In an attempt to predict variables important in contributing to the changes in the heart rate, multiple regression (all possible subset regression analysis) was used. Percentage change in the heart rate and difference in the heart rate from control values were each regressed on the independent variables (age, body weight, control heart rate, and the dose of atropine). The same procedures were repeated using log dose instead of the dose. The "best" subset model was selected using Mallows' coefficient (Cp) and R^2 criteria (6). Percentage change in heart rate and the set of independent variables containing the log dose was found to be the best-

Table 2. Atropine Dose, Control Heart Rate, and Heart Rate after Antagonism of Pancuronium-Induced Neuromuscular Blockade in Group B with a Mixture of Edrophonium 1.0 mg/kg and Different Doses of Atropine

Group B (n = 35)	Atropine dose (mg/kg)	Heart rate														
		Control	After reversal (minutes)													
			1	2	3	4	5	6	7	8	9	10	15	20	25	30
B-1 (n = 5)	0.020	85.6 (6.6)*	93.4 (8.1)	77.0† (6)	71.4† (6)	70.2† (5.8)	70.8† (5.7)	71.0† (6.3)	72.4† (6.6)	72.0† (6.6)	68.8† (5.6)	67.4† (5.9)	86.0 (7.8)	89.2 (5.5)	86.2 (6.9)	86.4 (7)
B-2 (n = 5)	0.0215	89.2 (3.3)	100.2† (4.1)	77.0 (5.6)	77.8† (4.6)	77.8† (5.2)	77.8† (4.5)	78.4† (4.3)	79.2 (4.3)	79.6 (4)	79.8 (3.9)	80.6 (3.8)	80.0 (3.8)	88.6 (6.5)	93.0 (7.1)	96.8 (8.7)
B-3 (n = 5)	0.023	86.4 (3.3)	108.8 (11)	90.4 (11.6)	86.4 (10.8)	84.2 (9.6)	83.6 (8.3)	82.4 (6.7)	80.2 (5.6)	79.4 (4.7)	79.0† (3.6)	78.6† (3.2)	75.8† (3.5)	90.8 (8)	84.4 (6.3)	86.2 (10.7)
B-4 (n = 5)	0.0245	72.8 (4)	82.2 (12.6)	73.2 (15)	68.2 (11.6)	64.8 (9.2)	63.0 (7.6)	62.0 (6.8)	62.0 (6.3)	62.4 (6.1)	61.8 (5.9)	62.4 (5.7)	68.0 (6)	70.2 (7.7)	77.2 (9.5)	76.4 (8.3)
B-5 (n = 5)	0.030	77.2 (4.5)	101.8 (11)	79.0 (14.4)	90.2 (13.2)	85.4 (11)	82.0 (10.1)	79.6 (8.7)	78.6 (8.2)	79.0 (7.9)	78.6 (7.3)	79.8 (7.8)	95.0 (7.9)	89.6 (9.1)	95.4† (4.6)	94.6 (5.7)
B-6 (n = 5)	0.035	80.2 (5.6)	92.6† (6.4)	82.0 (7.2)	80.6 (7.2)	81.0 (7.1)	82.0 (7)	81.6 (6.6)	82.8 (6)	81.2 (6)	82.0 (6.4)	82.0 (6.4)	87.8 (8.5)	92.0 (8.6)	94.2† (6.6)	93.2 (7.1)
B-7 (n = 5)	0.040	78.8 (6)	79.6 (10.1)	81.2 (10.4)	80.8 (10.3)	79.6 (10.1)	79.8 (9.7)	79.8 (9.5)	80.4 (9.1)	81.4 (8.9)	81.4 (8.6)	81.2 (8.9)	85.2 (9.8)	86.6 (11.5)	87.0 (9.9)	85.4 (8.4)

*Mean values (\pm SEM) are shown.†Different from control ($P < 0.05$).**Figure 1.** Dose-response curves for atropine 5 (—) and 10 minutes (---) after reversal.

fitted model between 5- and 10-minute intervals in both groups. In all of these models ANOVA for linearity was highly significant ($P < 0.01$), and at the same time the only significant factor contributing to the response was the log dose. Hence, we used simple regression analysis to determine the dose-response relation (percentage change in heart rate from the control value versus log dose) in both groups at 5 and 10 minutes. Regression lines in both groups were compared using analysis of covariance (7). We then tested for the difference between slopes of the two lines. This difference was found to be insignificant ($P > 0.32$) at 5 and 10 minutes. However, the test of

difference between elevations yielded a highly significant results ($P < 0.002$) at 5 and 10 minutes.

To compare the potency of atropine between the two groups, we calculated the ED_{50} and ED_{95} doses of atropine at 5 and 10 minutes. As defined, this is a quantal rather than a graded response, because the specified effect (the presence or absence of an increase in heart rate from the control value after the administration of the antagonistic mixture) is either present or absent (i.e., an all or none response). Patients were considered to have a positive or negative response based on this criterion. The ED_{50} and ED_{95} were calculated by fitting the number of patients with positive response at each dose level of atropine to a logit model (8) using PCNONLIN (9).

Using analysis of variance, we compared mean age and body weight among subgroups. Changes in heart rate in each subgroup were analyzed by a paired t -test. The incidence of arrhythmia was analyzed using Fisher's exact test. For all statistical comparisons, differences were considered significant when $P < 0.05$.

Results

All results were expressed as means (\pm SEM). There were no significant differences among the subgroups regarding patient's age, sex, or weight. The mean age was 29.6 (1.2) and 28.1 (1.3) years, and mean body weight 59.5 (1.6) and 62.6 (1.7) kg in groups A and B, respectively. The male/female ratio was 19/18 and 20/15 in groups A and B, respectively.

Table 3. The Calculated ED₅₀ and ED₉₅ Doses of Atropine at 5 and 10 Minutes after Administration of Atropine-Edrophonium Mixture in Groups A and B

	Edrophonium (group A) (0.67 mg/kg)		Edrophonium (group B) (1 mg/kg)	
	5 minutes	10 minutes	5 minutes	10 minutes
ED ₅₀ of atropine (mg/kg)	0.018	0.016	0.029	0.032
ED ₉₅ of atropine (mg/kg)	0.024	0.027	0.055	0.05

Changes in heart rate after administration of the mixtures are shown in Tables 1 and 2. The initial increase in heart rate was statistically significant in the subgroups A-5, A-7, B-2, and B-6. Subsequently, the heart rate decreased significantly in the subgroups A-1, A-3, B-1, B-2, and B-3 (Tables 1 and 2). The increase in heart rate in both groups at 15–30 minutes coincided with awakening of the patient and extubation.

There was a significant linear correlation between the log dose of atropine and the changes in heart rate (expressed as a percentage from preinjection control values).

The sample regression equations of the lines in group A at 5 and 10 minutes, and the *P*-value for the slopes were, respectively,

$$\begin{aligned} y &= 168.82 + 97.733x, & (P < 0.001) \text{ and} \\ y &= 139.34 + 80.821x, & (P = 0.002). \end{aligned}$$

In group B, the equations of the regression lines at 5 and 10 minutes, and the *P*-value for the slopes were, respectively,

$$\begin{aligned} y &= 93.109 + 62.671x, & (P = 0.02), \text{ and} \\ y &= 109.87 + 73.867x, & (P = 0.002). \end{aligned}$$

The regression lines for both groups at 5 and 10 minutes are in Figure 1. The test for significance of difference between slopes indicated that the regression lines did not deviate from parallelism (*P* > 0.32), but differed in position (*P* < 0.002).

ED₅₀ and ED₉₅ values of atropine after administration of atropine-edrophonium mixtures in both groups are shown in Table 3. The ED₅₀ of atropine when calculated at 5 minutes was similar to that at 10 minutes in each group. As expected, the ED₅₀ of atropine was 1.6–2 times greater in patients in group B, who received the higher dose of edrophonium (1 mg/kg), than in group A patients, who received a smaller dose of edrophonium (0.67 mg/kg). The calculated ED₉₅ doses of atropine at 5 minutes was

similar to that at 10 minutes in each group. Nevertheless, the ED₉₅ of atropine was 1.8–2.3 times greater in patients in group B than in patients in group A.

Arrhythmias were observed in eight patients in group A and two patients in group B (*P* = 0.0516) (Table 4). Arrhythmias resolved spontaneously without any treatment in all patients. Adequate reversal of neuromuscular block, as indicated by the presence of all four responses of TOF stimulation and a sustained contraction to a tetanic stimulus of 50 Hz, was achieved in all patients by the tenth minute after the administration of the antagonistic mixtures.

Discussion

One of the advantages claimed for use of edrophonium in reversal of nondepolarizing relaxant action in adults is that compared with neostigmine, less atropine is required to prevent bradycardia. Cronnelly et al. (10) reported that edrophonium requires about half the amount of atropine that is required when neostigmine is used. In that study (10), doses of neostigmine required to antagonize residual neuromuscular blockade (0.043 mg/kg) were higher than they were when edrophonium (0.5 mg/kg) was used. Recently, Breen et al. (11) reported that the dose-response curves for neostigmine and edrophonium were parallel and that neostigmine was 16 times more potent than edrophonium. The dose of edrophonium (0.67 mg/kg) employed in the present study is, therefore, equipotent to neostigmine 0.04 mg/kg.

Fogdall and Miller (12) examined equipotent doses of neostigmine and pyridostigmine (2.5 and 14.5 mg/70 kg, respectively) and found that atropine 1.0 mg/70 kg (i.e., 0.014 mg/kg) was required to prevent bradycardia. In the present study, a significant reduction in heart rate was noted after administration of an equipotent dose of edrophonium (0.67 mg/kg) with atropine 0.0155 mg/kg (Table 1). The implication is that edrophonium requires more atropine than is required when an equipotent dose of neostigmine is used, when both are administered according to the technique used in this study.

Several studies (5,13,14) have shown the edrophonium in doses between 0.5 and 0.75 mg/kg cannot be relied on to antagonize relatively profound blocks produced by pancuronium, atracurium, or vecuronium. In fact, Rupp et al. (5) suggested that the edrophonium dose should be at least 1 mg/kg to achieve antagonism as rapid in onset as when neostigmine 0.04 mg/kg is used at a time when twitch

Table 4. Type and Frequency of Arrhythmias

Drug combination	Frequency (%)	Type
<i>Group A</i>		
0.67/kg edrophonium + 0.014 mg/kg atropine	1/5 (20)	Wenchebach phenomena
0.0155 mg/kg atropine	2/5 (40)	Premature atrial contractions and A-V dissociation
0.017 mg/kg atropine	1/5 (20)	Premature atrial contractions
0.0185 mg/kg atropine	2/5 (40)	Premature ventricular contractions and bigeminy
0.02 mg/kg atropine	1/5 (20)	Premature atrial contractions
0.0215 mg/kg atropine	1/5 (20)	Premature atrial contractions
<i>Group B</i>		
1.0 mg/kg edrophonium + 0.0215 mg/kg atropine	1/5 (20)	Premature atrial contractions
0.0245 mg/kg atropine	1/5 (20)	Bradycardia (a heart rate <50 beats/min)

height is 2–10% of control. Gravenstein et al. (15) administered atropine and scopolamine (without anticholinesterases) to six normal human subjects. They noted that atropine and scopolamine were equipotent with respect to cardioacceleration and equally enhanced the effects of mephentermine on heart rate and blood pressure. Scopolamine had a faster onset and a shorter duration of action (15). In the present study, edrophonium altered the chronotropic response for atropine. A marked ($P < 0.05$) decrease in heart rate was observed after administration of edrophonium 1 mg/kg with atropine in doses <0.0245 mg/kg (Table 2).

We found that the dose–response curves for atropine (Fig. 1) were parallel for both doses of edrophonium employed in this study (0.67 and 1 mg/kg). The regression lines, however, differed significantly ($P < 0.01$) in position, being shifted to the left with edrophonium 0.67 mg/kg. This indicates the potency of atropine was greater in group A than in group B. The calculated effective median dose (ED_{50}) of atropine (Table 3) was 1.6–2 times higher in patients in group B, who received the higher dose of edrophonium (1 mg/kg), than in group A patients given a smaller dose of edrophonium (0.67 mg/kg). Similarly, the calculated ED_{95} doses of atropine have also been found to be 1.8–2.3 times greater in patients in group B than in group A patients.

A marginal initial increase in heart rate was observed after administration of atropine. This was significant in the subgroups A-5, A-7, B-2, and B-6 only. The marked initial increase in heart rate produced by atropine as reported by others (16) was not observed in the present study. All patients included in the present study were unconscious until 10 minutes after the administration of the reversal mixture. Many of the previous investigations were performed

during emergence from anesthesia when changing levels of consciousness, straining, and coughing may have increased heart rate. In this respect, our results are in accordance with that of Kongsrud and Sponhein (17).

The mode of administration of an anticholinergic drug (e.g., prior to or together with the anticholinesterase agent) is another aspect of the management of reversal of neuromuscular block. Several investigators studied the latter aspect. In fact, Fisher et al. (18) concluded that the cardiovascular changes can be minimized by administering atropine 30 seconds before edrophonium in infants and children. At the present time, opinions are still divided as far as the superiority of subsequent or simultaneous administration of atropine and the anticholinesterase agent (19). In clinical practice, the convenience of simultaneous injection of the two agents in one syringe appeals to many anesthesiologists.

Arrhythmias, including Wenchebach phenomena, premature atrial contractions, A-V dissociation, premature ventricular contractions, and bigeminy have been reported after combinations of edrophonium or neostigmine and atropine (16,20,21). We have observed similar arrhythmias in both groups (Table 4).

In the present study, the effects of various combinations of atropine and edrophonium have been examined. We found that the dose–response curves for atropine (after administration of the antagonistic mixture) were parallel for both doses of edrophonium employed in this study (0.67 and 1.0 mg/kg). The doses of atropine required to prevent bradycardia in 50% (ED_{50}) and in 95% of patients (ED_{95}) were higher in patients who received edrophonium 1.0 mg/kg compared with that in patients who received edrophonium 0.67 mg/kg.

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Respiratory Mechanics and Intrinsic PEEP during Ketamine and Halothane Anesthesia in Young Children

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Respiratory mechanics and intrinsic PEEP during ketamine and halothane anesthesia in young children. *Anesth Analg* 1988;67:656-62.

Static compliance of the respiratory system (C_{rs}) was measured by the interrupter technique in 18 anesthetized children to compare the effects of ketamine on C_{rs} with those of halothane. C_{rs} was the slope of the pressure-volume (P-V) curve obtained by repeated brief airway occlusions throughout relaxed expiration, and the intercept of the P-V curve on the pressure axis was the intrinsic positive end-expiratory airway pressure (PEEP_i). Expiratory time (T_e) was measured during a period of quiet breathing, and the passive expiratory time constant (τ) was measured during the relaxed expiration after an end-inspiratory occlusion. Nine children were anesthetized with a continu-

ous infusion of ketamine and a matching group of nine children inhaled halothane in oxygen. C_{rs} was significantly greater in the ketamine group (22.8 ± 6.2 ml/cm H₂O) than in the halothane group (15.7 ± 5.5 ml/cm H₂O). The τ value was also significantly greater in the ketamine group. Mean PEEP_i in the ketamine group was 2.3 ± 1.8 cm H₂O and in the halothane group was 0.4 ± 0.8 cm H₂O. PEEP_i correlated inversely with T_e/τ according to a logarithmic function. It was concluded that, in children anesthetized with ketamine, C_{rs} is significantly greater than that in children anesthetized with halothane, and the resultant prolongation of τ and decreased T_e/τ with ketamine anesthesia lead to increased PEEP_i.

Key Words: ANESTHESIA—pediatric. LUNG, MECHANICS—positive end-expiratory pressure. ANESTHETICS, INTRAVENOUS—ketamine. ANESTHETICS, VOLATILE—halothane.

Total respiratory compliance (C_{rs}) and functional residual capacity (FRC) decrease during anesthesia with most commonly used agents (1). These changes may be responsible for the arterial hypoxemia that continues into the postanesthetic period and may be deleterious to the patient (2). Therefore an anesthetic technique that preserves C_{rs} and FRC at preinduction levels would be desirable.

In previous studies of respiratory mechanics in anesthetized children, we noted that the time constant of a passive expiration (τ) was prolonged during ketamine anesthesia compared with halothane anesthesia (3). Because $\tau = R_{rs} \times C_{rs}$, where R_{rs} is the resistance of the respiratory system, we postulated that either R_{rs} was increased by ketamine, or C_{rs} , or both. The long τ found with ketamine anesthesia had

the effect of reducing the number of time constants during one expiratory time (T_e), with the result that there was insufficient time during expiration for complete emptying of the inhaled gas to the relaxed end-expiratory volume (V_{rs}). Thus FRC was maintained above V_{rs} and the magnitude of FRC- V_{rs} was inversely proportional to T_e/τ . This effect was minimal or absent in the children anesthetized with halothane. The elevated lung volume at end-expiration during ketamine anesthesia implies that transthoracic pressure is greater than zero at FRC. This phenomenon has been termed intrinsic positive end-expiratory pressure (PEEP_i) and has been measured in patients during acute and chronic respiratory illnesses who similarly showed prolonged τ (4-6). PEEP_i then should be greater in children anesthetized with ketamine than in those receiving halothane anesthesia.

In the present study, we have used a noninvasive method for measuring C_{rs} , R_{rs} , and PEEP_i in children anesthetized with ketamine and halothane to determine whether respiratory mechanics are preserved with ketamine anesthesia to a greater degree than with halothane.

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Methods

Subjects

Eighteen children from 13 to 83 months old who were scheduled to undergo elective surgery were the subjects for the study. All were ASA physical status class I, with no history of respiratory illnesses. The study received the approval of the Committee for Human Experimentation of our institution, and the parents of all children gave informed written consent before inclusion of the child in the study. The studies were carried out after induction of general anesthesia but before commencement of surgery.

Protocol and Anesthesia

Anesthetic techniques were similar to those reported in a previous study (3). Briefly, all children received premedication with triclofos orally 60–80 mg/kg 90 minutes before anesthesia. In two children (subjects 8 and 9 of the ketamine group) studies were carried out during sedation with triclofos and before induction of anesthesia. Nine children, including the children studied with sedation alone, were anesthetized with ketamine in a dose of 2 mg/kg IM followed by a continuous IV infusion of 0.01% ketamine in 5% dextrose in water up to a dose of 50–100 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. The subjects breathed room air throughout the test period.

A second group of nine subjects breathed 1–1.5% halothane in oxygen, at a flow of 250–300 $\text{ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$, from a Jackson-Rees modified Ayre's T-piece for induction and maintenance of anesthesia. Care was taken to prevent distention of the breathing bag to prevent inadvertent application of continuous positive airway pressure.

In all 18 children, measurements were carried out during anesthesia but before surgery. After completion of the studies, the elective surgical procedure commenced.

Pattern of Breathing and Expiratory Time Constant

The technique for measurement of these parameters has been previously described (3). While otherwise undisturbed, the subject breathed through a face-mask sealed at the edges with soft silicone putty. The proximal port of a pneumotachograph (Type F2, Mercury Electronics, Scotland) was attached to the mask and, in the halothane group, the distal port was connected to the anesthetic circuit. The two pressure outlets of the pneumotachograph were connected to

a differential pressure transducer (Validyne MP45) and the signal was amplified (Hewlett-Packard Amplifier 8805C) and integrated (Hewlett-Packard 8815A). The flow and volume (V) signals were displayed on an oscilloscope (Tektronix T935A) as well as recorded on magnetic tape (Hewlett-Packard Instrumentation Recorder 3964A) during 1 minute of quiet breathing. Zero flow was recorded after quiet breathing by occluding the distal port of the pneumotachograph, thus separating it from the fresh gas flow. The recorded signals were subsequently analyzed using an eight-channel paper recorder (Hewlett-Packard 7758B). T_e was measured from the interval between points of zero flow before and after expiration for alternate breaths during the 1-minute period.

Passive expiratory time constant (τ) was measured using the above apparatus with the addition of a differential pressure transducer and amplifier (as stated earlier) for measurement of mask pressure (P). After the period of quiet breathing, the distal port of the pneumotachograph was occluded manually at end-inspiration. When the pressure signal plateaued, the occlusion was released and the subsequent "relaxed" expiration was recorded. The volume signal from the subjects receiving halothane was corrected for the greater viscosity of oxygen in comparison with air by the method of Hobbes (7). The signals were subsequently analyzed by computer (PDP 11/23), which displayed the flow-volume curve for each occlusion and postocclusion expiration, allowing the operator to choose the linear portion. The inverse of the slope of the linear portion of the postocclusion expiration, as determined by linear regression of the flow-volume plot by the method of least squares, was τ . For each subject at least ten occlusions were performed, each separated by 15 seconds of quiet breathing. T_e/τ was then calculated and represents the number of time constants available in expiration.

Static Compliance by the Interrupter Technique

The static compliance of the respiratory system (C_{rs}) during expiration was calculated from the pressure-volume (P-V) curve obtained by measuring P and V during a series of brief interruptions of expiratory flow (8). During quiet breathing, at end-inspiration, the distal port of the pneumotachograph was manually occluded and when the mask pressure signal reached a plateau, the occlusion was released. During the subsequent "relaxed" expiration (Fig. 1), inter-

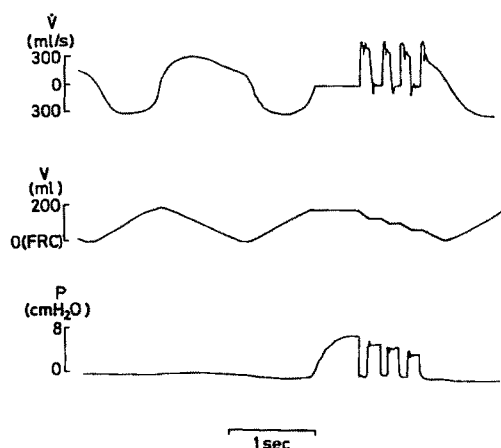


Figure 1. Flow (\dot{V}), volume (V), and pressure (P) signals from subject 1 from the halothane group during quiet breathing and during an end-inspiratory airway occlusion followed by brief interruptions of flow during the subsequent expiration.

ruptions of expiratory flow of approximately 100 milliseconds duration were performed by repeated manual occlusion of the distal port of the pneumotachograph until end-expiratory lung volume was reached. P and V were displayed and recorded as described earlier, and analyzed manually from the paper record. Only those interruptions in which P had a well-defined plateau of at least 100 milliseconds, indicating equilibrium of alveolar and mask pressure, were analyzed. During each interruption, the plateau pressure and corresponding V , corrected to BTPS, constituted a data point on the P - V curve (Fig. 2). In this way up to five points from each breath were plotted, and at least three breaths, separated by 30 seconds of quiet breathing, were analyzed.

The linear regression that best fit the data was determined by the method of least squares. C_{rs} was the slope of this line, and $PEEP_i$ was the intercept on the P axis. R_{rs} was calculated from π/C_{rs} . The Mann-Whitney U-test was used for comparison of anthropometric parameters τ , T_e/τ , C_{rs} , R_{rs} and $PEEP_i$ between the ketamine and halothane groups. A value of $\alpha < 0.05$ denoted statistical significance.

Determination of FRC

FRC was measured in eight of the nine children anesthetized with ketamine by the closed-circuit helium dilution apparatus as previously described (9). The final value for FRC was the mean of two or more measurements within 10% of each other. Specific compliance (sC_{rs}) was determined by dividing C_{rs} by FRC. FRC was not measured in the halothane group because this gas affected the helium analyzer.

Results

There was no significant difference between the ketamine and halothane groups in mean height (101 ± 17 and 99 ± 16 cm, respectively), weight (16.4 ± 5.4 and 16.5 ± 5.4 kg, respectively), or age (49 ± 24 and 44 ± 24 months, respectively).

The results of the FRC, C_{rs} , sC_{rs} , and $PEEP_i$ measurements are shown in Tables 1 and 2. Mean C_{rs} and $PEEP_i$ were significantly greater in the ketamine group than in the halothane group. Mean sC_{rs} in the ketamine group was 48.3 ± 12.7 ml·cm H_2O^{-1} ·L $^{-1}$. In the ketamine group the best correlation of C_{rs} (ml/cm H_2O) with parameters of growth was with age (months) according to the exponential equation

$$C_{rs} = 12.71e^{0.011 \times \text{age}}, \quad r = 0.97.$$

For the purpose of comparison with previous studies of C_{rs} during anesthesia, the regression of C_{rs} with height was determined and is shown graphically in Figure 3.

C_{rs} measured during sedation alone was similar to C_{rs} during anesthesia in each of the two children (subjects 8 and 9 from the ketamine group) in whom these measurements were carried out (Table 3, Fig. 2C).

The best correlation of C_{rs} (ml/cm H_2O) for the halothane group was with weight (kg) according to the equation

$$C_{rs} = 1.79 \times [\text{weight}]^{0.77}, \quad r = 0.72.$$

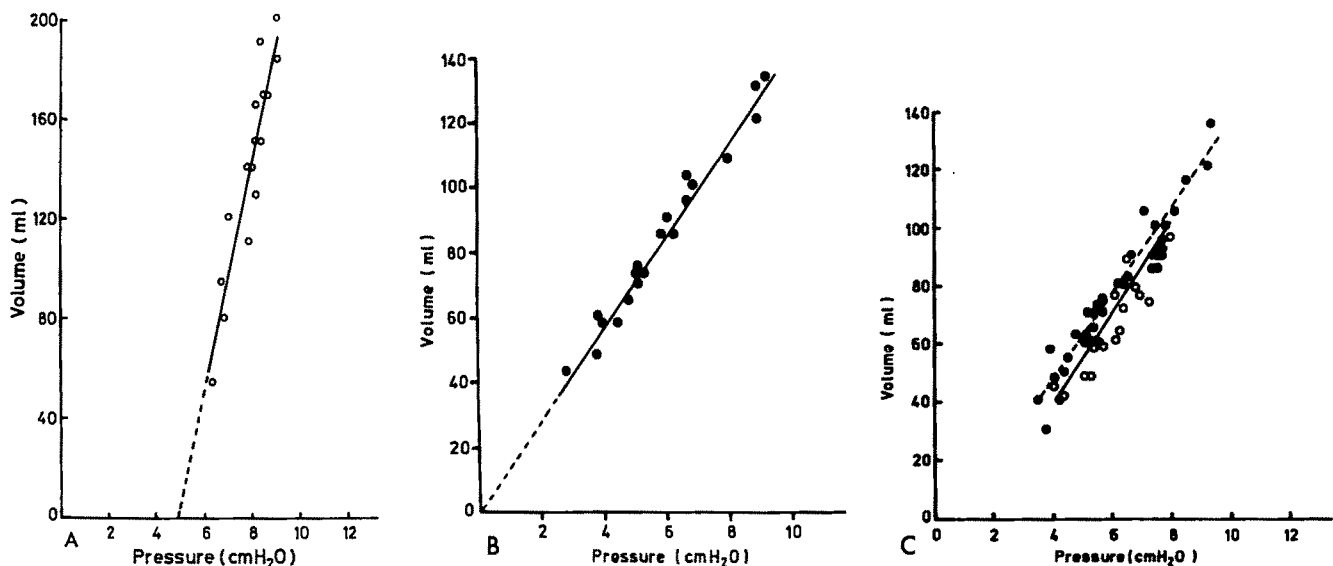
The correlation of C_{rs} with height in the halothane group is shown in Fig. 3.

τ was significantly longer in the ketamine group. R_{rs} was greater in the ketamine group (Table 1), although the difference just failed to reach significance at the 0.05 level. T_e/τ was significantly greater with halothane (2.7 ± 0.7) than with ketamine (1.9 ± 0.9). The regression of the correlation between $PEEP_i$ (cm H_2O) and T_e/τ for all subjects (Fig. 4) fit the logarithmic equation

$$PEEP_i = 3.27 - 2.56 \times \ln(T_e/\tau), \quad r = 0.75.$$

Discussion

We have shown that static respiratory compliance and $PEEP_i$ can be measured simply and noninvasively with a technique of brief airway interruptions throughout expiration during ketamine and halothane anesthesia in young children. C_{rs} and $PEEP_i$



during ketamine anesthesia were significantly greater than that measured during halothane anesthesia. R_{rs} , calculated from π/C_{rs} , was not significantly greater with ketamine, and thus the higher C_{rs} accounts for the longer τ with ketamine than during halothane anesthesia.

The interrupter method for measurement of lung mechanics was first applied during anesthesia by Gottfried et al. (8,10). The technique is based on the assumption that during a short occlusion of the airway during relaxed expiration, the mouth pressure represents static recoil pressure of the lungs (P_{st}). When the respiratory system is relaxed and sufficient time is available during an airway occlusion, alveolar pressure and P equilibrate and both equal P_{st} , which can then be conveniently estimated noninvasively by measuring P .

Jaeger (11) has shown that the relatively compliant cheeks and soft upper airway tissues may interfere with the rapid equilibration of airway pressure necessary in this test. This would result in underestimation of P , and therefore C_{rs} would be overestimated with the interrupter technique in the nonintubated subject (11) if the compliance of the gas in the extrathoracic airway and equipment (C_u) exceeds that of the lower respiratory system. To determine the minimum time necessary for adequate pressure equilibration in the upper airway of children in the age group studied here, we measured C_u in five additional children from 6 to 30 months old who were undergoing elective surgery with halothane anesthesia. Endotracheal intubation was carried out using a tube with a cuff inflated adequately to prevent leak of gas during positive-pressure ventilation. A Rendall-Baker mask of the type used in this study, but with an aperture for the endotracheal tube to pass through,

Figure 2. P-V curves: (A) From subject 2 from the ketamine group demonstrating $PEEP_i$, the intercept of the P-V curve on the pressure axis at FRC. (B) From subject 3 from the halothane group showing no significant $PEEP_i$. (C) From subject 9 from the ketamine group showing data from measurements during sedation (○) and during ketamine anesthesia (●). The regression lines are shown with the solid line representing sedation and the hatched line representing ketamine anesthesia.

was applied to the face and sealed with soft silicone putty. Pressure under the mask was then measured with a water manometer during injections of 1-ml increments of air up to 5 ml. A mask pressure-vs-volume increment curve was obtained and analyzed with linear regression analysis, which showed that the data fit a linear equation with $r > 0.93$ in all cases. C_u was then the slope of this line. The results are presented in Table 4. Mean C_u was 0.69 ± 0.42 ml/cm H_2O . This is much less than C_{rs} , and therefore only a small proportion of inhaled gas will be shunted to the oropharynx during the interruption of expiratory flow. Our C_u results are lower than C_u reported in adults (11), probably due to the smaller oral cavity in children as well as the stiff Rendall-Baker mask, which has a large surface of contact on the face. The wide variability in C_u has been noted in a previous study (11).

The time constant for equilibration of pressure in the upper airway (τ_{eq}) is the product of the airway resistance (R_{aw}) and C_u (4,11). R_{aw} is similar to R_{rs} , and mean R_{rs} for all subjects studied here was 0.03 cm $H_2O \cdot ml^{-1} \cdot sec^{-1}$. Thus τ_{eq} is approximately equal to $R_{rs} \times C_u$, and using the mean figures above, $\tau_{eq} = 21$ milliseconds. Thus, there are approximately 5 τ_{eq} s in the 100-millisecond pressure plateau, and there is sufficient time for equilibration of pressure in the upper airway.

Table 1. Respiratory Mechanics during Anesthesia

Subject	C_{rs} (ml/cm H ₂ O)	PEEP _i (cm H ₂ O)	τ (s)	T_e (s)	R_{rs} (cm H ₂ O·L ⁻¹ ·sec ⁻¹)
Ketamine					
1	21.0	2.8	0.92	1.64	43.8
2	33.1	4.7	2.33	1.26	70.4
3	29.1	1.5	0.99	1.58	34.0
4	19.9	1.7	0.70	1.33	35.2
5	21.8	2.0	1.18	1.67	54.3
6	23.5	0.9	0.37	1.43	15.7
7	27.5	1.3	0.51	1.27	18.5
8	15.7	5.5	0.76	0.97	48.1
9	14.0	0.1	0.43	0.93	31.0
Mean	22.8	2.3	0.91	1.34	39.0
SD	6.2	1.8	0.60	0.27	17.3
Halothane					
1	24.8	1.5	0.42	0.74	16.9
2	18.4	-0.4	0.40	1.24	21.7
3	13.8	0.0	0.29	1.03	21.0
4	14.3	0.4	0.30	0.99	21.0
5	23.4	0.9	0.65	1.15	27.8
6	15.0	1.5	0.27	0.96	18.0
7	11.4	0.2	0.47	1.04	41.2
8	11.1	0.6	0.33	0.90	29.7
9	8.9	-0.7	0.38	0.94	42.0
Mean	15.7*	0.4*	0.39*	1.00*	26.6
SD	5.5	0.8	0.12	0.14	9.5

*Significant difference as compared with the ketamine group ($\alpha < 0.05$).Table 2. FRC and Specific Compliance (sC_{rs}) in Subjects from the Ketamine Group

Subject	FRC (ml)	sC_{rs} (ml·cm H ₂ O ⁻¹ ·L ⁻¹)
1	402	52.2
2	500	66.2
3	962	30.2
4	400	49.8
5	652	33.4
6	567	41.5
7	537	51.1
8	254*	61.8
Mean	534	48.3
SD	212	12.7

*FRC measured after preanesthetic sedation before anesthetic induction.

Another factor that may delay equilibrium of alveolar and mouth pressures is activity of the inspiratory muscles during expiration. The use of an end-inspiratory occlusion, as described here, results in relaxation of the muscles of respiration, and the postocclusion expiration is passive (10,12). The presence of a plateau on the P signal is evidence that the above factors do not influence P, which is then a measure of P_{st} .

In using linear regression to analyze the P-V curve, we have assumed that C_{rs} does not change over the tidal volume range. There is experimental evidence to support this assumption (8,10,12) and the high correlation coefficients we obtained for linear regression of the P-V curve for each child (mean $r = 0.94 \pm 0.05$) support this.

It has been shown that compliance values obtained during anesthesia are influenced by the volume history of the subject and that prior inflation of the lungs to a known volume or pressure substantially increases the measured value. For this reason, in previous studies of compliance in healthy children during general anesthesia (13,14), a cuffed endotracheal tube was inserted and the volume history of the lungs was standardized by controlled inflations of the subjects' lungs preceding the measurement of C_{rs} . Because we intended to study C_{rs} during short surgical procedures with spontaneous breathing, we did not place endotracheal tubes and thus could not precede the measurements with known inflations. In spite of this, we have demonstrated a mean sC_{rs} of 48.3 ± 12.7 ml/cm H₂O (Table 2) from the children anesthetized with ketamine, which is similar to the mean sC_{rs} of 43.4 ml/cm H₂O for children 100-119 cm in height

Figure 3. Regression of C_{rs} (ml/cm H₂O) vs height (cm) for the subjects from the ketamine and halothane groups. The curves which fit the data best are described by the equations: ketamine: $C_{rs} = 0.04 \times [\text{height}]^{1.36}$, $r = 0.85$; halothane: $C_{rs} = 0.01 \times [\text{height}]^{1.57}$, $r = 0.71$. This is compared to the regression curves for C_{rs} vs height from two previous studies (13,14).

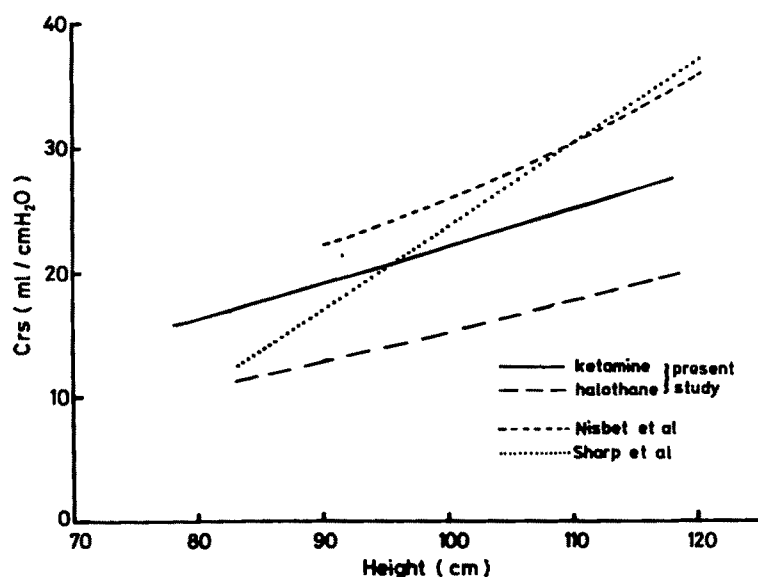


Table 3. Comparison of C_{rs} (ml/cm H₂O) Sedated vs Ketamine

Subject	C_{rs} sedated	C_{rs} ketamine
8	14.7	15.7
9	15.4	14.0

Table 4. Upper Airway Compliance (C_u)

Subject	Age (months)	C_u (ml/cm H ₂ O)
19	6	0.2
20	8	1.1
21	24	0.5
22	30	0.6
23	30	1.1

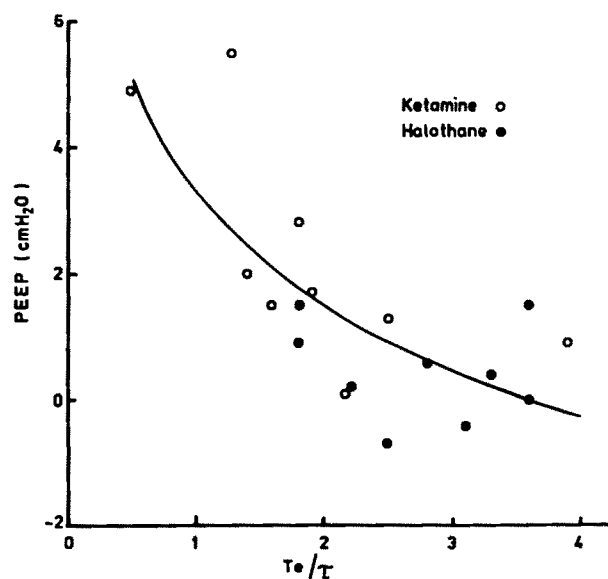


Figure 4. Relation of T_e/τ to PEEP, in all subjects. \circ denotes data from subjects from the ketamine group; \bullet denotes data from subjects from the halothane group.

from a study by Sharp et al. (14). Mean C_{rs} is also greater in the present study than C_{rs} from nonanesthetized children of similar age ventilated for neurologic illness or drug overdose (15). The regression curve of C_{rs} vs height from our study is similar to the curves from two previous studies of anesthetized,

paralyzed children (Fig. 3). Thus, ketamine preserves C_{rs} during spontaneous breathing at a level comparable to C_{rs} in children who are ventilated during anesthesia. The similarity of C_{rs} during sedation to that measured during ketamine anesthesia in two children in this study also suggests that ketamine has a sparing effect on C_{rs} . In contrast, C_{rs} is decreased during halothane anesthesia in comparison with the ketamine group (Fig. 3).

We have previously shown that FRC does not substantially change in young children on induction of anesthesia with ketamine (9) and subsequently demonstrated that the pattern of breathing is an important factor in maintaining FRC above V_{rs} during ketamine anesthesia (3). This is due to the prolongation of τ and increased T_i/T_e during ketamine anesthesia, and thus there is not sufficient time during a normal expiration for the lungs to completely empty before the start of the next inspiration. This phenomenon of dynamic elevation of FRC is also seen during mechanical ventilation when the respiratory rate is increased, thus decreasing T_e and hence the number of time constants available in expiration, T_e/τ , is decreased (16). Similarly, T_e/τ is decreased during spontaneous ventilation in patients with chronic air-

way obstruction in whom τ is prolonged (4). T_e/τ is then important in determining FRC in these states. When FRC is maintained above V_{rs} , the transpulmonary pressure does not return to zero at end-expiration, and intrinsic PEEP results. Because the magnitude of the ratio of T_e/τ is inversely proportional to the elevation of FRC above V_{rs} (3), the magnitude of PEEP_i is also determined by T_e/τ , and an inverse relation should be found between PEEP_i and T_e/τ . In this study we have demonstrated an inverse relation between PEEP_i and T_e/τ (Fig. 4).

The effect of an increase in PEEP_i is to improve oxygenation, probably by maintaining lung units open in the dependent regions of the lungs. A tendency for collapse of dependent lung units has been noted during anesthesia in children, in whom closing capacity is greater in relation to FRC than in adults, and this may have deleterious effects on the ability of the lungs to exchange gases (2). The presence of PEEP_i during ketamine anesthesia may prevent this collapse and contribute to the maintenance of normal Pao₂ even in the absence of supplemental oxygen (17). However, there is energy expenditure required to maintain PEEP_i in that the inspiratory muscles must develop a negative pressure greater than PEEP_i before inspiratory flow begins. In this way, PEEP_i can be considered an inspiratory threshold load (5). The presence of PEEP_i is also important when choosing a technique to measure C_{rs} . The determination of C_{rs} from a single point on the P-V curve, usually the end-inspiratory lung volume and the end-inspiratory occluded airway pressure (18), may underestimate C_{rs} in subjects during ketamine anesthesia with significant PEEP_i.

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Anesthetic Action of Opiates: Correlations of Lipid Solubility and Spectral Edge

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STONE DJ, DiFAZIO CA. Anesthetic action of opiates: correlations of lipid solubility and spectral edge. *Anesth Analg* 1988;67:663-6.

The ability of opiates to be a complete anesthetic has been assessed in animals. These studies have investigated the serum levels of opiate required to produce a decrease in anesthetic requirement for a concomitantly administered inhalation anesthetic. A linear dose-response relation has been observed between opiate serum level and reduction in anesthetic requirement up to the level of 50% reduction in minimum alveolar anesthetic concentration (MAC). These studies have not demonstrated the production of one MAC anesthesia by the opiates. Recent EEG studies have provided another means of comparing the central nervous system effects of opiates and inhalation anesthetics. The serum

levels of several opiates associated with a 50% reduction (IC_{50} or 50% inhibitory concentration) in maximal spectral edge frequency (SEF) have been reported. The free, unionized serum levels of each opiate at IC_{50} in humans or 50% MAC reduction in animals are remarkably similar. We calculated brain lipid opiate content at these serum levels using available physicochemical data. The calculated nanogram and molar brain lipid contents of the drugs fell within a 10-fold range while serum levels varied by 5000-fold. This similarity in membrane lipid content in association with EEG and anesthetic effects suggests that opiate "anesthesia" may involve a membrane effect in addition to the well established receptor interaction.

Key Words: POTENCY, ANESTHETIC—MAC. BRAIN, ELECTROENCEPHALOGRAPHY—spectral edge frequency. ANESTHETICS, INTRAVENOUS—opioids.

Opiates have been used as partial or complete anesthetics (1). The mechanism by which they produce an anesthetic effect has been related to both an action on opiate receptors and a possible effect on lipid membranes more commonly associated with inhalation anesthetics (2). Methods available to differentiate between these actions have been lacking in the past. Recent comments on anesthetic pharmacology noted that two essential, yet lacking, elements for a clinical application of opiate pharmacokinetics are "a reliable measure of the intensity of the drug action and a means of rapidly measuring (monitoring) drug concentrations in plasma or other biological specimens" (3). Electroencephalographic (EEG) studies have produced a useful quantitative monitor of opiate effects in the brain using spectral edge frequency (SEF) shift (4). The spectral edge frequency is defined as that frequency below which a certain percentage (usually

95%) of the total power (amplitude²) is located (4). The serum concentration of a drug required to cause half of the maximal SEF shift has been referred to as the IC_{50} (50% inhibitory concentration). Serum concentrations have also been measured at defined levels of central opiate effects using SEF measurements (5-7). Similarly, concentrations of opiates have also been measured for specific reductions in anesthetic requirements (MAC fractions) of inhalation anesthetics (8-12). This report correlates the observed plasma opiate concentrations at a specific SEF shift and reduction in inhalation anesthetic MAC for several species with the predicted brain lipid opiate concentrations calculated from the plasma opiate concentration.

Methods

Serum concentrations of fentanyl, alfentanil, and sufentanil that produce a 50% reduction in maximum SEF (IC_{50}) in man are shown in Table 1, as are the serum levels of fentanyl, morphine, and alfentanil required for a 50% MAC reduction for inhalation

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Table 1. Data Available from Previous Studies

Drug (species)	Serum concentration at 50% MAC reduction* (ng/ml)	Serum concentration at IC ₅₀ † (ng/ml)	Free un-ionized concentration (ng/ml)	Calculated brain lipid concentration		Molecular weight
				(ng/ml)	(mM)	
Fentanyl (humans) (5)	—	6.9	0.10	995	2.96	336
Fentanyl (dogs) (8)	6.0	—	0.09	860	2.56	—
Fentanyl (dogs) (11)	2.0	—	0.03	287	0.85	—
Alfentanil (humans) (5)	—	520	37.0	540	1.71	316
Alfentanil (rat) (10)	771	—	54.9	785	2.54	—
Sufentanil (humans) (7)	—	0.74	0.01	89	0.23	—
Sufentanil (rats) ‡	0.97	—	0.01	125	0.32	386
Sufentanil (dogs) (12)	0.7	—	0.01	89	0.23	—
Morphine (rats) (10)	195	—	31.4	188	0.66	285
Morphine (predicted in humans)	—	200	30	190	—	—

*MAC is minimum alveolar anesthetic concentration for inhalation anesthetics.

†IC₅₀ is the serum concentration required to cause half of the maximal spectral edge frequency shift (50% inhibitory concentration).

‡DiFazio CA, Lake CL, Unpublished data.

Table 2. Physicochemical Data

	Morphine	Fentanyl	Sufentanil	Alfentanil
pKa	8.0	8.4	8.0	6.5
% un-ionized pH 7.4	23	9	20	89
Free fraction (unbound)	70	16	7	8
Octanol: water partition coefficient un-ionized drug	6	9,550	8,930	14.5*

*This value represents the value reported by Meuldermans, et al. (13) and differs from the value in subsequent texts quoting his work.

anesthetics in animals. We have data to suggest that the serum sufentanil level required for a 50% MAC reduction in the rat is 0.97 ng/ml as noted in Table 1. The physicochemical properties of the opiates are shown in Table 2. The coefficients used in the table were calculated from Meuldermann's original data for alfentanil, fentanyl, and sufentanil (13). The alfentanil value of 14.5 actually reported by Meulderman differs from the value of 145 commonly quoted in subsequent texts (3). The free un-ionized drug concentration is assumed to be constant in all aqueous phases in the body because this form rapidly crosses cell membranes. This concentration was calculated as the product of the serum drug concentrations, the percent free fraction of the drug, and the percent of the drug present in its un-ionized form at body pH using the drug pKa and the Henderson-Hasselbach equation. Brain lipid opiate concentration was then calculated by multiplying the calculated free un-ionized opiate concentrations by the octanol:water partition coefficients for the un-ionized drug. The values calculated for free un-ionized drug concentrations and brain lipid concentrations for IC₅₀ and 0.5 MAC are shown in Table 1.

Results

In reviewing the available data, it is apparent that the serum drug levels at 50% MAC reduction for experimental animals (rats and dogs) in past experiments are remarkably similar to those associated with a 50% reduction in SEF (IC₅₀) for humans (Table 1). Furthermore, calculating free serum concentrations of the un-ionized opiate drug associated with the 50% MAC reduction and IC₅₀ results in remarkably similar values for each agent. Small differences in brain lipid concentration between agents were observed in spite of an enormous difference in drug lipid solubility and potency: while there is approximately a 5000-fold range in the free unionized drug concentration in serum between the various opiates associated with these changes, the differences are markedly reduced to 10-fold when brain lipid concentrations are calculated.

Discussion

Although extensive analyses of the effects of opiates on the EEG have been carried out, they do not describe a simple and potentially useful correlation between drug level and anesthetic depth as does the spectral edge frequency (14-19). Spectral edge frequency has also provided a method of gauging the depth of halothane anesthesia and the pharmacodynamics of thiopental (4,21). Analysis of enflurane's effect on SEF is more complex due to the high frequency activity seen with this anesthetic (4).

In view of the possible association between EEG effect and serum drug levels, it is remarkable to find that the serum concentration of a drug required to

produce a 50% reduction of maximal SEF in humans is so similar to that which produces a 50% MAC reduction in animals. For the opiates described in this report, a linear dose-response relation exists for MAC reduction up to 50%. The effect of opiates beyond this point is limited in that either a ceiling effect for the opiate on MAC reduction has been observed, or further measurements could not be carried out because movement could not be used as the end point for response to stimulation with high doses of opiates because they produced rigidity or nonepileptic motor activity (21,22). However, the ability of the opiate to reduce anesthetic requirement for potent agents up to the 50% MAC level and to shift EEG power in a manner similar to that seen with halothane suggests that the term "anesthesia" should be ascribed to them (4).

Is the ability of opiates to produce such a fraction of anesthesia and their effect on a highly derived aspect of the EEG merely a fortuitous coincidence? In an attempt to answer this question, we extended the data by calculating the absolute and molar theoretical brain lipid content of the opiates associated with this MAC reduction and SEF shift. Brain lipid opiate content calculated for the four drugs is remarkably similar considering that these were observed in different species and massive differences in potency (and administered dose) between the least potent (morphine) and most potent (sufentanil) opiate are present. The similarity in drug brain lipid content and effect for these agents is striking and suggestive of a lipid-phase anesthetic mechanism. The differences noted between agents may also reflect the choice of the octanol:water partition coefficient as an approximation of actual brain lipid solubilities.

While most aspects of the mechanism of general anesthesia are still in question, the Meyer-Overton theory relating lipid solubility and anesthetic potency strongly suggests a lipophilic site of action. This report does not mean to suggest that the anesthetic capability of opiates is merely a function of lipid solubility, but we suggest that the similarities in the calculated amount of opiate dissolved in brain lipid at a defined level of anesthesia and EEG effect is thought-provoking. This mathematically derived brain lipid opiate level might be thought of as the "functional lipid solubility" of the drug. For instance, from the available data, one might predict that the IC_{50} for spectral edge shift for morphine would occur in humans when serum morphine content is 200 ng/ml.

The CNS opiate effect is believed to represent an action of opiate on a protein opiate receptor, and this interaction is reversible with naloxone (11). The pos-

sibility that opiates produce anesthesia via a nonopiate receptor mechanism was considered by Dodson and Miller (2) who found that loss of righting reflex induced by a leucine-enkephalin analogue in an amphibian was reversible by the application of pressure. Other investigators (23,24) observed that the relative population of opiate receptors (μ - and κ -) in the brain differs widely between species and that only a small fraction of the opiate receptors (25%) are occupied by opiates when opiate anesthesia is produced in rats. The additional observations in the present report demonstrating an interspecies similarity in producing anesthetic effects at a constant brain lipid opiate concentration suggests a possible lipid membrane site of action for opiate anesthesia. Such an effect in a lipid phase would suggest that the opiate receptor is associated with or within a lipid phase.

Although the ability of opiates to produce anesthesia and the very definition of anesthesia are open to question, it is clear that some opiates can produce more than the 50% MAC reduction used as the basis for comparison in this report. Clinically, high doses of opiates have produced a stable cardiovascular state, analgesia, and a low level of awareness associated with major surgery carried out with these agents alone. However, considerable questions exist in humans and animals on the completeness of anesthesia with high dose opiates. In animal studies, a ceiling effect on the amount of anesthesia produced is observed at some level above a 50% MAC reduction. Perhaps this ceiling effect occurs because the relatively large narcotic molecular does not alter the hydrophobic phase of the cell membrane as completely as do the nonpolar hydrocarbon molecules of the inhalation anesthetics. Other possible explanations included limited efficiency of the opiate at drug receptors and, possibly, poor coupling of opiate to receptor substrate. At this time, we cannot assess the relative contributions of receptor versus lipid action of opiates as anesthetics. However, the observation of this report that there is a relation between the calculated brain lipid membrane concentrations of opiates with a defined MAC reduction and EEG change strongly suggests a lipid membrane site for the anesthetic action of opiates at least up to the 50% MAC reduction level.

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Effect of Hypothermic Hemodilutional Cardiopulmonary Bypass on Plasma Sufentanil and Catecholamine Concentrations in Humans

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OKUTANI R, PHILBIN DM, ROSOW CE, KOSKI G, SCHNEIDER RC. Effect of hypothermic hemodilutional cardiopulmonary bypass on plasma sufentanil and catecholamine in humans. *Anesth Analg* 1988;67:667-70.

The effect of hypothermic hemodilutional cardiopulmonary bypass (CPB) on plasma sufentanil and catecholamine concentrations was studied in four groups of ten patients each, receiving four different doses of sufentanil. Samples for measurement of sufentanil were obtained before CPB, at 15, 30, and 45 minutes of CPB, during rewarming, immediately after and 15, 60, and 240 minutes after CPB. In addition, in groups III and IV, which received the highest dose of sufentanil, blood samples were also obtained for measurement of plasma levels of epinephrine and norepinephrine. Sufentanil concentration decreased in all groups with the start of CPB (group I, 2.92 ± 0.2 to 2.04 ± 0.2 ; group II, 3.30 ± 0.3 to 1.51 ± 0.2 ; group III, 7.08 ± 0.7 to 3.45 ± 0.3 ; group IV, 10.33 ± 0.5 to 4.59 ± 0.5 ng/ml). No further decreases occurred during CPB but in-

creases occurred with rewarming. The first measurement after CPB approached the concentration before CPB (group I, 2.82 ± 0.3 ; group II, 2.56 ± 0.5 ; group III, 4.42 ± 0.4 ; group IV, 6.10 ± 0.4 ng/ml). Norepinephrine concentrations demonstrated a wide variability with no significant changes. Epinephrine levels increased significantly during rewarming in both groups (group III, 141 ± 23 to 279 ± 79 pg/ml; $P < 0.05$; group IV, 105 ± 24 to 267 ± 68 pg/ml, $P < 0.05$). The stability of plasma sufentanil concentrations during CPB suggest that no measureable metabolism or excretion occurred. The increase with rewarming and after CPB suggest significant sequestration. The increase in plasma epinephrine levels with rewarming, when sufentanil concentrations were also increasing, make it unlikely that any clinically acceptable concentration of sufentanil is capable of preventing this response.

Key Words: ANESTHETICS, INTRAVENOUS—sufentanil. SYMPATHETIC NERVOUS SYSTEM—catecholamines. SURGERY—cardiovascular.

High doses of fentanyl or sufentanil are commonly used for both induction and maintenance of anesthesia during cardiac surgical procedures. The intense analgesia produced by these potent opioids is effective in blunting most hemodynamic and hormonal responses to surgical stimulation (1-3). We have been particularly interested in the "stress" hormonal response which occurs during the period of cardiopulmonary bypass (CPB) (4).

Very high doses of fentanyl appear unable to

prevent the increases in a variety of hormones including vasopressin or catecholamines during CPB (1,2). Sufentanil has been reported to be more effective than fentanyl in attenuating the "hormonal" response prior to but not during CPB (5,6). One possible explanation may lie in the effect of CPB on the pharmacokinetics of these opioids. Plasma levels of fentanyl decrease precipitously with initiation of CPB and then continue to decline gradually to levels lower than might be attributed to hemodilution alone (7). Fentanyl may be absorbed by the extracorporeal circuit (7) or sequestered in the lungs (8,9). Continued metabolism and excretion cannot be ruled out through hepatic and renal blood flow are decreased since levels after CPB are significantly below those before CPB (7,9). This continued decrease in plasma fentanyl concentrations may lead to levels inadequate for anesthesia, particularly during the periods of rewarming and immediately after CPB (7,10).

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Table 1. Sufentanil Concentrations in Groups I-IV*

	Group I	Group II	Group III	Group IV
Before CPB	2.92 ± 0.2	3.30 ± 0.3	7.08 ± 0.7	10.33 ± 0.5
During CPB				
15 min	2.04 ± 0.2†	1.51 ± 0.2†	3.45 ± 0.3†	4.59 ± 0.5†
30 min	2.08 ± 0.2†	1.56 ± 0.2†	3.28 ± 0.3†	4.22 ± 0.3†
45 min	2.08 ± 0.2†	1.51 ± 0.2†	3.32 ± 0.3†	4.31 ± 0.3†
60 min	2.32 ± 0.7† (n = 7)	1.47 ± 0.2† (n = 7)	3.75 ± 0.3† (n = 8)	4.26 ± 0.3† (n = 7)
Rewarmed	2.51 ± 0.2†	1.70 ± 0.2†	3.63 ± 0.3†	4.72 ± 0.4†
After CPB				
15 min	2.82 ± 0.3	2.56 ± 0.5†	4.42 ± 0.4†	6.10 ± 0.4†
60 min	2.28 ± 0.2†	1.89 ± 0.2†	3.91 ± 0.3†	5.49 ± 0.5†
240 min	1.63 ± 0.2†	1.60 ± 0.2†	3.46 ± 0.3†	4.41 ± 0.4†
	1.14 ± 0.3† (n = 5)	0.99 ± 0.2† (n = 7)	2.85 ± 0.5 (n = 4)	2.60 ± 0.4 (n = 5)

*± SEM.

†P < 0.05 before CPB.

This study was designed to determine the changes in plasma sufentanil concentrations produced by hypothermic hemodilutional CPB. We assumed that plasma sufentanil levels would decrease in a manner similar to that seen with fentanyl (7). A range of doses at or above the clinically recommended levels were examined. We hoped to relate changing sufentanil concentrations to changes in plasma catecholamine concentrations during CPB, hypothesizing that the "stress" response associated with CPB would be least in patients with the highest levels of sufentanil.

Methods

Forty patients scheduled for elective coronary artery surgery were studied. Written informed consent was obtained from each patient and the study was approved by the Institutional Review Board.

Patients were randomly allocated to one of four treatment groups: group I received a single dose of sufentanil of 30 µg/kg; group II received 10 µg/kg loading dose followed by an infusion of 0.05 µg/kg⁻¹/min⁻¹; group III received 20 µg/kg plus infusion of 0.1 µg/kg⁻¹/min⁻¹ and group IV received 40 µg/kg plus infusion of 0.2 µg/kg⁻¹/min⁻¹. The infusion of sufentanil was discontinued just prior to the institution of CPB. All patients were cooled during CPB to 25°C (nasopharyngeal) utilizing a Bentley Bos 10 bubble oxygenator with 2 L of Ringer's lactate for priming.

Radial arterial blood samples for determination of plasma concentrations of sufentanil were obtained at nine points: 1) immediately prior to CPB; 2-4) every 15 minutes during CPB for the first 45 minutes; 5) during rewarming at 35°C; 6) immediately after CPB; 7-9) 15, 60 and 240 minutes after CPB. In patients on

CPB for more than one hour, an additional sample was obtained at 60 minutes. In five patients in both groups III and IV, samples were drawn to determine catecholamine concentrations (epinephrine and norepinephrine), before CPB, at 15, 30, and 45 minutes on CPB, during rewarming, immediately after CPB and again at 15 minutes after CPB.

Samples were drawn into glass tubes, iced immediately and the plasma separated in a refrigerated centrifuge and then stored at -70°C for later assay. Plasma epinephrine and norepinephrine concentrations were determined by radioenzymatic assay (11) and sufentanil in duplicate by radioimmunoassay assay (12). The sufentanil assay was highly specific and had a sensitivity of 0.1 ng/ml. Intra- and interassay coefficients of variation were less than 5%. Intra-group data were analyzed with a correlated *t*-test and intergroup data by analysis of variance. *P* < 0.05 was considered statistically significant.

Results

The patients in all four groups were comparable for age, sex, degree of disease, preoperative medications and operative procedure.

Table 1 summarizes the sufentanil data. There was an initial significant decrease in sufentanil concentrations in all groups following institution of CPB. (I—2.92 ± 0.2 to 2.04 ± 0.2; II—3.30 ± 0.3 to 1.51 ± 0.2; III—7.08 ± 0.7 to 3.45 ± 0.3; IV—10.33 ± 0.5 to 4.59 ± 0.5 ng/ml). For the remainder of the period of hypothermia plasma concentrations were stable. With rewarming plasma concentrations of sufentanil increased significantly in all groups when compared to the concentrations measured at 45 min. of CPB: (GP.I—2.08 ± 0.2 to 2.51 ± 0.2; GP.II—1.51 ± 0.2 to

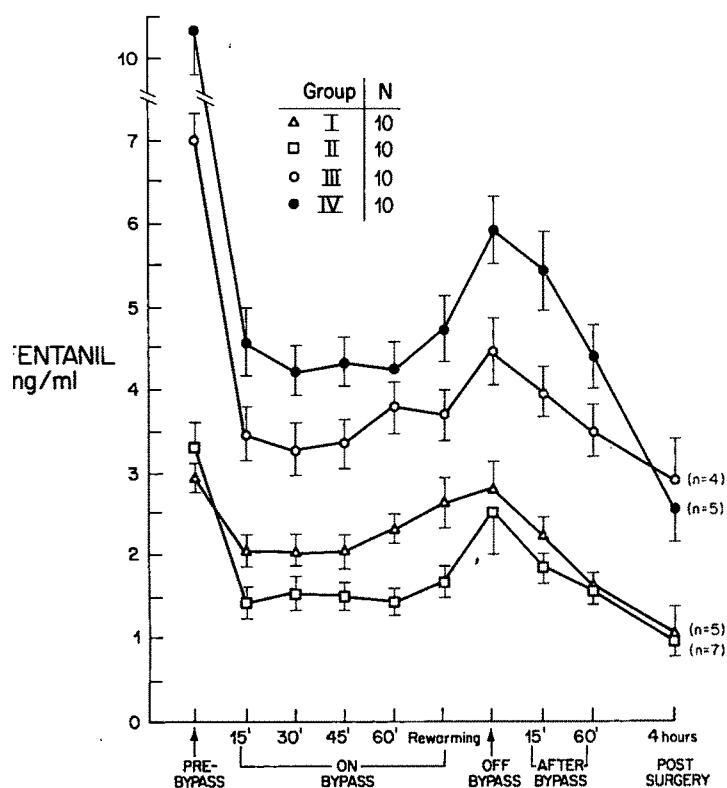


Figure 1. Plasma sufentanil concentrations in all four groups. All measurements represent the mean \pm SEM for ten patients except for the last sample, 4 hours (240 minutes) after CPB. Statistically significant changes are noted on Table 1.

1.70 ± 0.2 ; GP.III— 3.32 ± 0.3 to 3.63 ± 0.3 ; GP.IV— 4.31 ± 0.3 to 4.72 ± 0.4 ng/ml). The initial sample, immediately after CPB showed a further significant increase in all four groups, approaching the concentration of sufentanil is the pre-CPB sample. This is illustrated graphically in Fig. 1. In Group I the concentrations before and after CPB were not significantly different (Table 1).

The catecholamine responses to CPB were similar in groups III and IV (Table 2). There were wide variations in individual norepinephrine responses. On the average, gradual increases occurred but these did not achieve statistical significance. There was a statistically significant increase in epinephrine in both groups with rewarming. However, individual changes in plasma sufentanil and epinephrine concentrations were not significantly correlated for either group ($r = 0.100$).

Discussion

Our data suggest that sufentanil disposition during hypothermic CPB differs from that previously reported for fentanyl. Previously published data for

fentanyl demonstrate a marked decrease in plasma concentrations with the institution of CPB and a continued gradual decline not attributable to hemodilution and sequestration alone (7). Whether fentanyl is absorbed by the bypass circuit (7) sequestered in the lungs, or metabolized and excreted (8,10), at the end of CPB plasma fentanyl concentrations are considerably below the pre CPB levels (7,8,10). Bentley et al have suggested that fentanyl concentrations remain relatively constant during CPB (8). However, in Bentley's group of five patients, the concentrations of fentanyl after CPB were still markedly below pre-CPB levels (17.3 ± 1.2 to 10.4 ± 0.8 ng/ml; $P < 0.001$).

The data from our study of 40 patients demonstrate a striking stability of plasma sufentanil concentrations during CPB with concentrations after CPB approaching those obtained prior to CPB. This pattern holds true over a wide range of clinically relevant concentrations. The initial decrease in plasma sufentanil concentrations is expected on the basis of hemodilution and an altered volume of distribution. Once hypothermic CPB is established, however, elimination appears to be negligible. Several factors account for this. Sufentanil is rapidly metabolized by N-dealkylation at the piperidine nitrogen, and O-methylation (13). The decreased body temperature during CPB should markedly reduce or halt this metabolic process. In addition, hepatic clearance of sufentanil is high (hepatic extraction ratio 0.7). Decreased liver blood flow that occurs during CPB will affect extraction and this may be an especially significant factor.

Our data also may indicate that relatively large amounts of sufentanil are sequestered during hypothermic CPB. Absorption by the bypass circuit itself is unlikely to be a major factor given the significant increases post CPB. It is likely, as with fentanyl, that significant pulmonary sequestration may occur, since pulmonary perfusion and ventilation are restored with rewarming and washout can then occur. It is not possible from this study to determine if sequestration also occurs in other organ systems which have markedly reduced perfusion during hypothermia. It is clear, however, that with rewarming and reperfusion, one can expect increases, not decreases in plasma sufentanil concentrations.

The number of catecholamine samples obtained was relatively small, and subject to the usual high individual variability. Nevertheless, a statistically significant increase in plasma epinephrine occurred during rewarming—the point at which sufentanil concentrations were increasing. The enormously high concentrations of sufentanil measured in Groups III

Table 2. Catecholamine Concentrations in Groups III and IV*

	Group III		Group IV	
	Epi (pg/ml)	Nor epi (pg/ml)	Epi (pg/ml)	Nor epi (pg/ml)
Before CPB	141 ± 23	464 ± 68	105 ± 24	427 ± 104
During CPB				
15 min	248 ± 25	528 ± 94	149 ± 16	371 ± 62
30 min	340 ± 109	911 ± 470	208 ± 86	389 ± 74
45 min	279 ± 104	880 ± 325	185 ± 53	566 ± 120
Rewarmed	279 ± 79†	798 ± 224	267 ± 68†	632 ± 192
After CPB				
15 min	159 ± 32	471 ± 46	265 ± 126	497 ± 153
15 min	141 ± 21	424 ± 51	124 ± 20	566 ± 168

*± SE Mean.

†P < 0.05 vs before CPB.

and IV suggest to us that it is unlikely that any clinically acceptable concentration of sufentanil is capable of preventing this response. It is likely that the catecholamine responses during CPB are not related to the adequacy of "analgesia". We believe they represent humoral responses to other stimuli (viz. hemodynamic changes, hemodilution, or hypothermia) which are not blunted by anesthetic doses of synthetic narcotic analgesics.

The concentrations of sufentanil reported in this study do not necessarily reflect true levels of biologically active unbound drug. It has been reported that sufentanil is over 90% bound to plasma proteins (mainly alpha-1 acid glycoprotein) at normal pH [14]. Protein binding may increase significantly when the pH is lowered, as may occur during CPB. With the institution of hemodilutional bypass the concentrations of albumin and alpha-1 acid glycoprotein are substantially reduced but the total amount should remain unchanged and thus not affect the levels of free drug. This study did not address that issue nor did we attempt to assess the biological activity of free sufentanil during CPB.

In conclusion, the decrease in plasma sufentanil concentrations that occurs with the institution of CPB may be explained primarily by the effect of hemodilution with sequestration probably playing a significant role. The stability of sufentanil concentrations during CPB and increase with warming and removal from CPB argue against continued metabolism and exception. In this respect, sufentanil appears to differ from fentanyl.

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Alterations in the Course of and Histopathologic Response to Influenza Virus Infections Produced by Enflurane, Halothane, and Diethyl Ether Anesthesia in Ferrets

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TAIT AR, DU BOULAY PM, KNIGHT PR. Alterations in the course of and histopathologic response to influenza virus infections produced by enflurane, halothane, and diethyl ether anesthesia in ferrets. *Anesth Analg* 1988;67:671-6.

Alterations in the course of and histopathologic response to influenza viral infections by halothane, enflurane, and diethyl ether anesthesia were evaluated in ferrets. There were no significant differences in the incidence and duration of lethargy, pyrexia, rhinorrhea, or sneezing in infected animals given one of the three anesthetic agents under

investigation, compared with those receiving no anesthesia. There were no differences in lung pathology in infected animals given one of the three anesthetic agents, or no anesthesia, though histopathologic changes in the nasal turbinates were significantly greater in ferrets given enflurane. This study suggests that general anesthesia administered to ferrets infected with influenza virus carries minimal morbidity, although enflurane anesthesia was found to produce greater histopathologic changes than the other agents.

Key Words: ANESTHETICS, VOLATILE—halothane, enflurane, diethyl ether. INFECTION—influenza.

Information regarding the effects of anesthesia on the immune response and the infectious process is sparse. Clinically such information is important, because it addresses the issue of whether or not to proceed with elective surgery in the patient who presents with an acute infection. In the past, most case reports and clinical studies have suggested that the presence of an acute infection, particularly one of viral origin, be a contraindication for elective procedures (1-3). More recent studies have, however, suggested that for certain minor procedures postponement of surgery due to the presence of a mild viral infection is unnecessary (4,5). Animal studies investigating the effects of anesthesia on the infectious process have also been somewhat equivocal and, in general, have focused on anesthetics that are no longer clinically used (6-8).

In an attempt to further assess the impact of

anesthesia on the infectious process, we have designed an animal study utilizing inhalation anesthetic agents used commonly in current practice. Earlier work from this laboratory using a mouse model suggested that different anesthetic agents administered to animals infected with influenza virus carried differing mortalities (9). Influenza virus-induced mortality in mice is an excellent method of examining virus virulence and correlates well with viral virulence in the human population. In humans, however, influenza is primarily an infection of the upper respiratory tract whereas, in mice, the principal pathology lies in the lower respiratory tract.

The ferret has been used extensively in studies investigating the pathogenicity of influenza viruses (10-12). The pattern of infection in this animal closely parallels that seen in humans in that infection is usually localized in the upper respiratory tract and is characterized by pyrexia, sneezing, rhinorrhea, and lethargy. Lung involvement is occasionally present but minimal (13,14). Although symptoms are naturally difficult to quantify, the ferret has been used in this way to evaluate the effectiveness and/or pathogenicity of live attenuated influenza vaccines before human use (15). For these reasons the ferret was

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chosen as our animal model for the investigation of the effects of anesthesia on influenza virus infections.

Materials and Methods

Animals

Fifty-three male and female ferrets, 8–10 weeks old and weighing 400–800 g, were used. The experimental protocol was in accordance with guidelines approved by the University of Michigan Institutional Animal Investigation Committee. The ferrets were obtained, pathogen-free, from Marshall Research Animals, North Rose, New York. The animals were housed in stainless steel cages and fed Purina Lab Chow and water ad libitum. Thirty-six ferrets were randomly selected for exposure to the influenza virus; the remaining 17 served as noninfected controls.

The Virus

Type A influenza virus (A/Puerto Rico/8/34) was obtained from Dr. Hunein Maassab at the Department of Epidemiology in the School of Public Health, University of Michigan. Selection of this virus was based on its clinical similarities in man and ferret (13).

Exposure of Ferrets to Influenza Virus

Infection was achieved by exposing the animals to small-particle viral aerosol produced by nebulizing a suspension of 5 ml of a $10^{2.5}$ dilution of the A/PR/8/34 influenza virus. The virus was delivered by a Bird aerosol apparatus and directed through a glass and steel chamber with exhaust ports at the opposite end. Each animal was placed in the infection chamber and exposed to the viral aerosol for 15 minutes. Rectal temperatures of all ferrets, infected and noninfected, were measured once per day using a calibrated thermistor (Yellow-Springs). Temperatures were measured at the same time of day to avoid normal diurnal temperature fluctuations. In addition, all ferrets were examined daily for evidence of rhinorrhea, lethargy, coughing, and sneezing. Lungs were auscultated daily. Infected and noninfected ferrets were kept separate at all times, care being taken to standardize room temperature, provision of food and water, and time of observation. Animals were housed three to a cage.

Exposure of Ferrets to Anesthesia

Four days after viral inoculation, the infected group was further divided and randomly assigned to one of

four groups: those receiving no anesthesia ($n = 9$), and those exposed to either diethyl ether, halothane, or enflurane ($n = 9$ in each group). In addition, three noninfected ferrets were included in each anesthetic group. The remaining eight served as noninfected, nonanesthetized controls. Anesthesia was not administered until the fourth day after viral exposure to allow the virus to establish itself. Toms et. al. (13), using a ferret model, demonstrated high virus titers in nasal washings and peak titers in lung washings on day 4. Francis and Stuart-Harris (10), using a similar model, showed that by day 4 there were marked histologic changes, including polymorphonuclear infiltration of the submucosa and epithelium thickening. In addition, Knight et. al. (9) showed that day 4 marked the onset of any appreciable mortality in mice.

The anesthetic agents were administered in equipotent concentrations (approximately 1 MAC), from either a Dräger or an Ethrane vaporizer, or a Boyles bottle. Anesthetic vapors were directed into a glass and steel exposure chamber at a constant flow of 5 L/min in air. Anesthetic concentrations within the chamber were determined at steady state using a GOW MAC gas chromatograph. Each ferret was exposed to a particular anesthetic for a period of 1 hour, which resulted in a period of unconsciousness lasting approximately 55 minutes.

Histopathology Methods

Two days after anesthesia, a random sample of one-third of the infected ferrets were killed, along with all anesthetized controls. The animals were weighed and their lungs removed and weighed separately. The nasal turbinates were removed and visually examined. Both lungs and nasal turbinates were fixed for histologic examination after the method of Francis and Stuart-Harris (10). The remaining ferrets were observed daily for a further 4 days for evidence of morbidity. All animals and histologic specimens were coded so that observers were blind to both group and exposure. Histologic specimens were read by a staff veterinary pathologist. The severity of histopathologic changes in the lung was given an overall score of 1 through 4: 1) no pathology, 2) epithelial pseudostratification, 3) epithelial desquamation, and 4) purulent bronchiolitis. Further analysis was based on evidence of interstitial pneumonia and intra-alveolar hemorrhage. Histologic examination of the nasal turbinates utilized a similar grading system as follows: 1) no pathology, 2) septal thickening and/or focal infiltration of mononucleocytes

(MNs) and polymorphonuclear leucocytes (PMNLs), 3) patchy infiltration of MN's and PMNLs, and 4) diffuse infiltration. In addition, the mucosal exudate from the turbinate lumen and the submucosa were analyzed for evidence of PMNL and MN infiltration.

Statistics

Comparison of the incidence rates for respiratory symptoms was by χ^2 analysis. Analytical variables such as the duration of the clinical findings and frequency of temperature spikes were analyzed using analysis of variance. Significance, unless stated otherwise was achieved at the 5% level ($P < 0.05$). All data were expressed as mean \pm S.D.

Results

The severity of the clinical findings were studied, as well as the histologic examination of the lungs and nasal turbinates.

Clinical Findings

The incidence of sneezing was 53.3% in the infected group and 17.6% in the uninfected group. This difference was statistically significant. Also, the duration of sneezing was significantly longer in the infected group (mean 1.38 days \pm 0.59) than in the uninfected group (0.17 \pm 0.39). The incidence and duration of sneezing in the infected group, however, were not significantly different in ferrets given different anesthetic agents or in those that received no anesthesia at all.

Interestingly, comparison of the incidence rates of sneezing in the uninfected ferrets demonstrated that those animals receiving diethyl ether sneezed significantly more often ($P < 0.001$) than either the animals given halothane or enflurane or those given no anesthesia at all. The duration of sneezing in the infected group, however, was no different than it was for the unanesthetized ferrets or for those given anesthetics.

The incidence of rhinorrhea in the infected groups was 100%, which was significantly greater than in the noninfected ferrets, which had an incidence rate of 35.3%. The mean duration of rhinorrhea in the infected groups was significantly longer than in the noninfected groups: 3.87 \pm 1.34 vs 0.88 \pm 1.3 days. Animals that were not infected did not have rhinorrhea for any more than 1 day.

There was no significant difference in the incidence or duration of lethargy between infected and

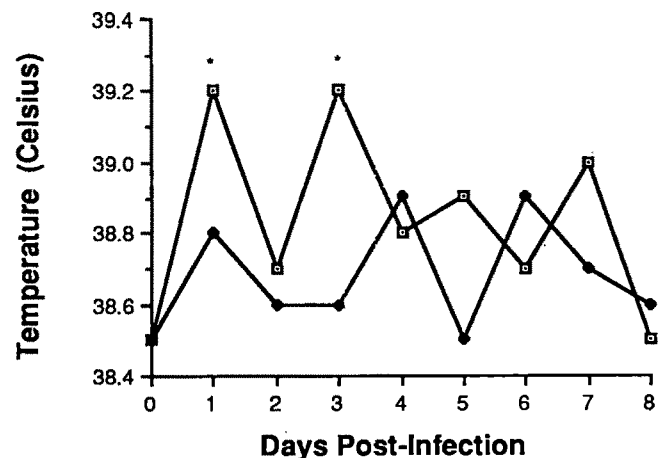


Figure 1. Illustration of a typical temperature profile for an unanesthetized infected ferret (\square) and an unanesthetized uninfected ferret (\blacklozenge) to demonstrate the presence of fever spikes characteristic of influenza infection. *Fever spikes in the infected ferret of $\geq 0.7^\circ\text{C}$ above preinfection temperature.

noninfected groups, nor were there any differences in lethargy in each of the different anesthetic groups.

Ferrets infected with influenza virus had significantly more days with a fever $> 39.2^\circ\text{C}$ (normal temperature in ferrets is 38.7°C) than did the noninfected animals. In addition, the infected ferrets demonstrated the presence of fever spikes characteristic of an influenza virus infection. A fever spike is defined as an increase in rectal temperature of $\geq 0.7^\circ\text{C}$ above preinfection temperature (11). Fever spikes were not observed in uninfected animals. The pattern of fever spikes in the infected animals was not altered by the use of different anesthetic agents. An illustration of the distribution of fever spikes in an unanesthetized infected animal is shown in Figure 1.

Histopathology

Histopathologic examination of the lungs of the ferrets showed no significant changes in the trachea, bronchi, or lung interstitium between uninfected anesthetized animals and infected animals (anesthetized or not). Nevertheless, a very small number of animals demonstrated a mild patchy or diffuse pneumonia. This was seen in the infected groups with or without anesthesia.

Histopathologic examination of the nasal turbinates demonstrated mucosal changes involving PMNL and MN infiltration, evidence of epithelial regeneration, and epithelial necrosis with or without epithelial sloughing. PMNL infiltration of the mucosa, as well as evidence of epithelial regeneration, was more frequent in the infected group with or

Table 1. Histopathology of the Nasal Turbinates in Infected Ferrets

Anesthesia	Epithelium			Other	
	Necrosis	Sloughing	Regeneration	Exudate	PMNLs+MNs in submucosa
None	○	○	++	+	+
Halothane	○	+	++	+	+
Enflurane	++	++	+	++	++
Diethyl ether	○	○	+	+	+

Histologic scores are expressed as median values. ○, no pathology; +, mild pathology; ++, moderate/severe pathology.

without anesthesia than it was in the corresponding uninfected animals. Influenza-infected animals given enflurane anesthesia had significantly more epithelial necrosis and sloughing than did the unanesthetized animals or those given the different anesthetic agents. PMNL and MN infiltration of the submucosa was also more severe in the enflurane anesthetized virus infected group (see Table 1). All other groups of infected and uninfected animals had minimal epithelial necrosis, or none at all, and minimal PMNL and MN infiltration of the submucosa.

Discussion

Influenza viruses belong to the family *Orthomyxoviridae* and, as such, are some of the most important respiratory viruses in terms of morbidity and mortality in humans. The importance of influenza as a disease lies not so much in its clinical manifestation, but in its propensity for epidemic and, indeed, pandemic spread. Because of the tendency of influenza to occur in epidemics, it is highly likely that patients may present for anesthesia and surgery with preclinical or subclinical influenza infections. Because the decision to proceed with surgery in the face of acute viral infection is controversial and is associated with both medical and economic considerations, it seemed appropriate to evaluate the effect of anesthesia on this virus in an animal model.

The ferret provides a useful model for the study of influenza virus pathogenicity because it closely mimics the pathogenicity observed in humans, i.e., it produces an infection with pyrexia and fever spikes that is predominantly confined to the upper respiratory tract (13). Seeding of the virus to the lower respiratory tract has been observed, but is limited (13,14). Ferrets infected with the A/PR/8/34 influenza virus strain demonstrated typical influenza-like symptoms including lethargy, sneezing, rhinorrhea, and pyrexia. Results from this study demonstrate that the incidence and duration of respiratory findings in infected animals were not significantly dif-

ferent between anesthetized and nonanesthetized ferrets. None of the three anesthetic agents evaluated was associated with any increase in respiratory morbidity. The observation that diethyl ether produced significantly more sneezing in the uninfected ferrets than the other agents suggests the role of diethyl ether as an airway irritant, and its propensity for the stimulation of respiratory secretions (15). That the duration of sneezing in this group was not longer than 1 day supports this view.

The absence of lung pathologic changes observed in this study has been described elsewhere. Toms et al. (13), in comparing different clones of a recombinant form of this virus, found negligible to slight histologic damage despite consistent lung infection. The influenza strain A/PR/8/34 is, however, much more damaging to the nasal turbinates. Toms et al. (13) described a superficial desquamation of the ciliated and goblet cells that was followed by a PMNL exudate and subsequent cell regeneration. Francis and Stuart-Harris described an acute phase marked by epithelial necrosis and desquamation with exudation from, and inflammation of, the submucosa. The onset of repair was observed 4 days postinfection, progressing rapidly through the 6th to the 14th day (10). Our findings observed on the sixth day after exposure are consistent with these former studies, although the extent of histopathologic changes (other than in the enflurane-treated animals) was not as marked. Similarly, the histopathologic changes in the nasal turbinates were not as extensive as might be expected in human influenza infections. The observed differences in our model may be reflective of both the mode of virus exposure and the strain of virus used. In the past, studies comparing human and ferret influenza infections have utilized intranasal inoculation that does not mimic natural exposure to the virus (11-13). Aerosol inoculation theoretically provides a more uniform distribution of the virus because it produces particles of different sizes, which facilitates dissemination of the virus to both the upper and lower respiratory tracts (16). Intranasal inoculation tends to concentrate the virus inoculum

on the nasal mucosa, and this may result in a more extensive histopathologic response. Although our findings appear consistent with other studies utilizing the A/PR/8/34 virus, the use of a variety of influenza strains and/or clones makes comparisons between studies difficult to assess.

Despite the small sample used in our study it is interesting to note the more marked histopathologic change observed in the enflurane group as compared to the other groups. This was characterized by PMNL and MN infiltration of the submucosa with evidence of significant epithelial necrosis and sloughing. It is somewhat surprising that the histologic changes associated with enflurane were more severe than those associated with diethyl ether, because clinically the latter is more of an airway irritant. The difference, however, may be due to a difference in the way enflurane alters the immune response, rather than a result of a direct irritant effect on the respiratory tract.

The appearance of PMNLs demonstrates the activation of the defense process and the initiation of the inflammatory response. PMNLs, together with macrophages (monocytes) and eosinophils, are primarily responsible for phagocytosis. These cells kill and digest microorganisms using a combination of low pH, enzymatic action, and the production of highly potent oxygen radicals. Graham showed as early as 1911 that phagocytosis by human and rabbit leukocytes is inhibited by diethyl ether anesthesia (17). More recently, halothane anesthesia has been shown to inhibit PMNL chemotaxis, phagocytosis, and bacteriocidal activity (18,19). Enflurane anesthesia, however, may act differently than halothane anesthesia in terms of PMNL motility and function. Mathieu's laboratory (20) demonstrated a dose-dependent inhibition of chemotaxis at concentrations of 1-4% halothane. Enflurane at concentrations of 1-7%, on the other hand, appeared to stimulate chemotaxis, resulting in an increase in PMNL movement of as much as 14% (20). In a subsequent study evaluating the effect of anesthesia on human leukocyte phagocytic and microbicidal functions it was shown that, whereas halothane decreased the production of myeloperoxidase and lysozyme, enflurane (and isoflurane) stimulated their production (20). Nakagawara et al., however, demonstrated inhibition of superoxide production by halothane, enflurane, and isoflurane that was thought to result in part from a decrease in the mobilization of intracellular Ca^{2+} (21). Other aspects of the immune response may also respond to anesthetic exposure. For example, anesthetics have been shown to decrease B-lymphocyte and antibody production, although preformed antibodies appear to be unaffected (22). Cellular events may also be inhibited,

including lymphocyte transformation and cell-mediated toxicity (23,24). In terms of the initial inflammatory response, however, the apparent stimulatory effect of enflurane on PMNL activity may partially explain the abundance of these leukocytes in the submucosa and in the exudate of the turbinate lumen. If, indeed, myeloperoxidase and lysozyme activity is enhanced by enflurane, then this could partially explain the observed increase in epithelial necrosis and sloughing and the minimal degree of regeneration observed in the enflurane treated animals.

It is also interesting to note that histologic examination of the noninfected anesthetized ferrets revealed a greater degree of exudate in the lumen of the turbinates of animals that received enflurane and diethyl ether than for the other agents. Most of this exudate was identified as mucus, which is consistent with the clinical observation that these agents (particularly diethyl ether) stimulate the production of respiratory tract secretions (15). On the other hand, as might be expected, halothane produced no mucosal exudate in the airways.

The findings of this study suggest that the administration of general anesthesia to influenza-infected ferrets does not result in an increase in respiratory morbidity. These findings are in contrast to early animal studies by Shope (7), who showed that diethyl ether administered to ferrets infected with swine influenza virus increased the severity of the disease, compared to unanesthetized infected ferrets. Dubin (8), however, found no difference in the severity of disease in swine influenza-inoculated mice anesthetized with diethyl ether or intraperitoneal pentobarbital. More recently, Knight et al. (9) found that enflurane produced significantly less respiratory histopathologic changes and morbidity than did halothane, diethyl ether, or pentobarbital. That this latter observation is not entirely consistent with our present findings leads us to postulate that this may reflect the different target organs for the virus in mice and in ferrets. For example, murine pulmonary involvement was far more extensive than observed in the ferret, where infection of the nasal turbinate is the predominate pathology.

In an attempt to evaluate the impact of anesthesia on the infectious process in terms of histopathology and course of infection, we have designed an animal model that closely mimics the type of influenza infection observed in humans. This study demonstrates that anesthesia administered to influenza infected ferrets carries no increase in respiratory morbidity. The observations that the histopathology of enflurane-anesthetized infected ferrets was signifi-

cantly greater than for other agents may suggest different actions of this agent on the defense process. It is hoped that this study will prompt further evaluation of the mechanisms by which the volatile anesthetic agents affect the immune response and the clinical manifestation of infection.

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Neurologic Outcome in Aged Rats After Incomplete Cerebral Ischemia

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BAUGHMAN VL, HOFFMAN WE, THOMAS C, MILETICH DJ, ALBRECHT RF. Neurologic outcome in aged rats after incomplete cerebral ischemia. *Anesth Analg* 1988;67:677-82.

The effect of age on outcome after induced cerebral ischemia was tested in rats. Cerebral ischemia was produced by unilateral carotid ligation and hemorrhagic hypotension to 30 mm Hg (moderate ischemia) or 25 mm Hg (severe ischemia) in young (6 month) and old (26-28 month) rats anesthetized with 1 MAC halothane. Young rats had significantly better neurologic outcomes than old rats after similar ischemic challenges. This advantage disappears, however, when the inspired oxygen tension is altered to produce similar P_{aO_2} in both age groups during ischemia.

Measures of regional CBF with radioactive microspheres showed a 70% decrease in cortical blood flow in the ischemic cerebral hemisphere in both young and old rats. Plasma glucose concentrations increased from 150 to 250 mg/100 mL during ischemia in both age groups. Histologically, the brains showed similar signs of focal ischemic damage in striatum, hippocampus, and cortex in young and old rats. These results indicate that when blood pressure and respiratory factors are controlled experimentally during ischemia, young and aged rats have similar neurologic outcomes after cerebral ischemia.

Key Words: BRAIN—blood flow. AGE—cerebral function.

Aging is accompanied by a slow and progressive decline in multiple body systems. There is, however, disagreement concerning the effects of aging on the central nervous system. Several authors (1,2) have reported a continual decline in cerebral blood flow (CBF) and metabolism in the elderly, whereas others (3,4) have shown little or no decline in these parameters in healthy geriatric subjects without evidence of cardiovascular or neurologic disease. Theories explaining brain aging include depression of metabolic rate and glycolytic turnover, appearance or accumulation of agents such as free radicals known to produce neuronal injury, and loss of cortical neurons or neurotransmitter function (5-7). It has been proposed

that these anatomic, physiologic, and biochemical changes may place aged neurons at greater risk during ischemia. To study whether the aged organism is at greater risk for neuronal damage from stroke, we studied neurologic outcome and mortality in young and aged rats using a model of incomplete cerebral ischemia. Blood pressure and respiration were controlled during the ischemic period to eliminate their potentially confounding effects.

Methods

Forty-six young (6 months) and 26 old (26-28 months) male Sprague-Dawley rats weighing 350-450 g were used in these studies. The old rats correspond physiologically in age to human patients approximately 72 years old. For surgery, rats were intubated and ventilated with anesthetic levels of halothane. A MAC level of 1.1% inspired halothane was used for young rats and 0.8% for aged rats (8). Catheters were inserted into the right femoral artery and vein for continuous blood pressure recording and drug administration and into the right subclavian vein for blood withdrawal. The right carotid artery was iso-

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lated, and a loose ligature was placed around it for later clamping. At the completion of surgery the rat was allowed to stabilize for 30 minutes before initiation of ischemia.

Outcome Studies

Two graded levels of cerebral ischemia were studied. Cerebral ischemia was produced by the combination of carotid occlusion and hemorrhagic hypotension to a mean arterial pressure 30 mm Hg (moderate) or 25 mm Hg (severe) for 30 minutes. The mean blood pressure was recorded digitally and maintained at the prescribed hypotensive level ± 2 mm Hg. The inspired oxygen fraction was 0.3 for the moderate and 0.2 for the severe ischemic challenge. At the end of the ischemic period the carotid was unclamped, and the withdrawn blood was slowly reinfused into the rat over 10 minutes. After a 30-minute reinfusion/recovery period the catheters were removed, the incisions closed, and the rat extubated.

All rats were maintained in individual cages with free access to food and water. The cages were maintained in a temperature- and light-dark-controlled environment during the postischemic, neurologic evaluation period. It was found at the end of these outcome studies that young rats had significantly higher P_{aO_2} levels than old rats given the same inspired oxygen fraction. Therefore, two additional groups of young rats were similarly tested at the moderate and severe ischemic challenges with P_{aO_2} adjusted to levels seen in the older animals. Rectal temperature was maintained at 37°C and P_{aCO_2} between 35 and 45 mm Hg by adjusting ventilation. Vecuronium was administered as needed to maintain paralysis. Arterial pH was maintained at normal levels by bicarbonate infusion.

Neurologic deficits were first evaluated 3 hours after recovery and then every 8 hours for 3 days. Deficits were scored from 0 to 5 as follows: 0 = normal, 1 = paw adduction or unusual posture, 2 = circling behavior and unilateral weakness, 3 = stroke-related seizures induced by stimulation, 4 = unstimulated seizures, 5 = death associated with progressive stroke.

Histopathology

Histologic examination of brain tissue was performed using additional groups of rats for each ischemic condition ($n = 4$ per group and ischemic level). Eighteen hours after ischemic recovery the rats were anesthetized with halothane and killed by transcatheter

perfusion with 50 ml of saline followed by 50 ml of 10% buffered formalin. Although neuronal damage progresses over several days, 18 hours was chosen to obtain histologic tissue under all treatment conditions before the rats died of ischemic injury. The brains were dissected out and immersed in 10% formalin for 1-2 weeks. The forebrain and hindbrain, including the cerebellum, were sliced into coronal blocks, which were embedded in paraffin wax, and 7-8- μ m sections were cut and mounted on slides. These slides were stained with hematoxylin-eosin and examined in a blinded manner by a neuropathologist using light microscopy. Brain histopathology was graded in the ischemic hemisphere on a four-point scale: 0 = no observable neuronal damage; 1 = scattered neuronal death; 2 = moderate focal damage in hippocampal, striatal, and cortical areas; 3 = severe damage involving extensive neuronal tissue; 4 = total infarct.

Electroencephalography and Plasma Glucose

In separate tests EEGs were recorded and plasma glucose measured in young and old rats ($n = 6$ per group). In addition to the surgery indicated earlier, the skull was exposed and screw electrodes were inserted above the right cortex for bipolar EEG recording. The EEG was recorded in these rats under baseline halothane anesthesia after 15 minutes of right carotid occlusion and hypotension to 30 mm Hg, after an additional 15 minutes of hypotension at 25 mm Hg, and 30 minutes after reinfusion of blood and recovery. The inspired oxygen fraction ($F_{I_{O_2}}$) was 0.3 at 30 mm Hg and 0.2 at 25 mm Hg in aged rats, and the $F_{I_{O_2}}$ was adjusted in young rats to produce comparable levels of P_{aO_2} . Blood samples were taken for plasma glucose measurement at each of the test conditions in these rats. The samples were centrifuged, and plasma glucose was measured using a Yellow Springs glucose analyzer.

Cerebral Blood Flow

Cortical CBF was measured in young and old rats ($n = 4$ per group) under three separate test conditions: baseline (1 MAC halothane anesthesia), during moderate ischemia (30 mm Hg hypotension), and during severe ischemia (25 mm Hg hypotension). Rats were prepared as described earlier. The left ventricle was catheterized via the right carotid artery, using pressure pulses to monitor proper catheter placement. At the completion of surgery the anesthetic concentration was maintained at 1 MAC halothane for a 30-

minute stabilization period. The first microsphere test was made under control conditions. The mean blood pressure was then decreased to 30 mm Hg by phlebotomy. A second CBF determination was made 15 minutes after the start of the ischemic period. A third and final microsphere test was performed 15 minutes after lowering the blood pressure to 25 mm Hg.

Microspheres

Fifteen-micrometer microspheres labeled with cobalt 57, tin 113, and scandium 146 (New England Nuclear) were used in these studies. Stock solutions containing 500,000 microspheres/ml were suspended in isotonic saline with 0.01% Tween-80. Microspheres were vortexed for 1 minute, and 0.2 ml (100,000 microspheres) was withdrawn, injected into the left ventricle (dead-space = 0.06 ml), and flushed in with 0.2 ml saline over 20 seconds. Starting immediately before each microsphere test and continuing for 45 seconds after the end of each injection, blood was withdrawn from a femoral artery at 0.4 ml/min. Mean arterial blood pressure was measured continuously from the femoral artery catheter to ensure that blood pressure did not change appreciably during the microsphere test.

At the end of the third microsphere test, each rat was killed, and the brain was removed, sectioned into left and right cortical and subcortical samples, and weighed. Cortical tissue typically contained a small percentage (<10%) of white matter. The activity of each microsphere in brain and blood samples was analyzed using a Nuclear Chicago 1035 gamma counter and a Nuclear Data 600 multichannel analyzer. CBF was measured according to the methods of Heymann et al. (9).

Statistics

Data are reported as mean \pm SE. Nonparametric neurologic deficit data were compared using a Mann-Whitney U test and a test of proportions of two means for mortality. Parametric data were analyzed using a two-way analysis of variance with repeated measures. Differences between means involving multiple tests were compared using Scheffe's tests.

Results

Changes in arterial blood pressure, heart rate, and arterial blood gas tensions during ischemia are shown

in Table 1. Two levels of ischemia were produced, one at 30 ± 2 mm Hg (moderate) and one at 25 ± 2 mm Hg (severe), but at 30 mm Hg young rats had higher P_{aO_2} levels when ventilated with the same inspired oxygen (30%) than did old rats. Therefore, a second young group (young corrected) was tested, in which P_{aO_2} was corrected to the same level as in old rats. The same was also done during hypotension to 25 mm Hg with an inspired oxygen concentration of 20%.

Neurologic outcomes after unilateral cerebral ischemia are shown in Figure 1. Both young and aged rats showed stroke-related deficits and mortality that were significantly more severe after hypotensive levels of 25 mm Hg than following levels of 30 mm Hg. Young rats had statistically significantly fewer deficits and lower mortality rates than did old rats when the inspired oxygen was the same in both groups, but these age-related differences were abolished by decreasing P_{aO_2} levels in young rats to the same levels as in old rats. EEGs during halothane anesthesia showed high-amplitude slow wave activity consistent with the anesthetic state (Fig. 2). Aged rats showed somewhat more EEG depression during ischemia than young rats, but recovery of brain electrical function was similar for both groups.

CBF, shown in Figure 3, decreased more in the right cerebral hemisphere ipsilateral to carotid ligation during these hypotensive challenges than it did in the left, contralateral hemisphere. Young and old rats had similar CBF values during halothane anesthesia and the two levels of ischemia. Plasma glucose increased in both young (P_{aO_2} -corrected) and old rats during ischemia and returned to control levels during recovery (Fig. 4). These changes were similar for young and old rats.

Histologic examination of brains revealed focal ischemic damage in hippocampus, striatum, and cortical regions, which was almost exclusively located in the right (ischemic) hemisphere. Both young P_{aO_2} -corrected and old rats showed these focal lesions, and both the severity and the extent of ischemic damage were more closely related to the level of ischemia (25 vs 30 mm Hg) than to the age group. Aged rats had a histopathologic score of 1.7, indicating moderate damage at moderate ischemia (30 mm Hg) and 3.0 at a severe ischemia (25 mm Hg), indicating more extensive neuronal damage. Young rats had histopathologic scores of 1.5 at 30 mm Hg and 3.3 at 25 mm Hg, suggesting ischemic-induced neuronal damage similar to that in aged rats.

Discussion

The present results indicate that when blood pressure

Table 1. Cardiovascular and Blood Gas Tensions in Young and Aged Rats During Ischemia

Group Treatment	n	Blood pressure (mm Hg)	Heart rate (beats/min)	Paco ₂ (mm Hg)	Pao ₂ (mm Hg)	Arterial pH
Moderate Ischemia						
Aged						
Control	8	96 ± 6	290 ± 13	41.9 ± 3.4	78 ± 9	7.37 ± 0.02
30 mm Hg		30 ± 1*	323 ± 18	40.3 ± 1.8	81 ± 15	7.36 ± 0.01
Recovery		93 ± 7	353 ± 12	46.1 ± 2.4	88 ± 13	7.36 ± 0.02
Young						
Control	10	99 ± 4	355 ± 18	37.5 ± 1.6	117 ± 6†	7.41 ± 0.02
30 mm Hg		30 ± 1*	298 ± 11	34.3 ± 1.9	155 ± 5*,†	7.38 ± 0.02
Recovery		96 ± 2	339 ± 6	39.9 ± 1.4	117 ± 8†	7.42 ± 0.02
Young corrected‡						
Control	8	96 ± 6	308 ± 11	37.1 ± 1.0	73 ± 5	7.42 ± 0.01
30 mm Hg		30 ± 1*	323 ± 18	36.9 ± 0.9	84 ± 3	7.37 ± 0.01
Recovery		99 ± 4	357 ± 10	39.0 ± 1.5	65 ± 2	7.40 ± 0.01
Severe Ischemia						
Aged						
Control	8	91 ± 4	303 ± 9	42.4 ± 4.1	63 ± 5	7.36 ± 0.03
25 mm Hg		25 ± 1*	313 ± 12	39.1 ± 2.9	68 ± 4	7.37 ± 0.02
Recovery		80 ± 8	326 ± 9	43.8 ± 3.9	61 ± 5	7.34 ± 0.03
Young						
Control	10	80 ± 5	302 ± 8	37.1 ± 1.0	92 ± 4†	7.41 ± 0.01
25 mm Hg		25 ± 1*	304 ± 13	37.1 ± 1.1	101 ± 3†	7.34 ± 0.02
Recovery		100 ± 3	356 ± 11	42.5 ± 1.0	69 ± 3	7.39 ± 0.02
Young corrected‡						
Control	8	91 ± 5	288 ± 4	37.1 ± 1.5	74 ± 5	7.43 ± 0.03
25 mm Hg		25 ± 1*	356 ± 23	35.6 ± 1.5	77 ± 3	7.39 ± 0.01
Recovery		77 ± 4	368 ± 13*	38.5 ± 0.9	63 ± 5	7.42 ± 0.01

Data reported as mean ± SEM.

*P < 0.05 compared to control within each group.

†P < 0.05 young compared to aged.

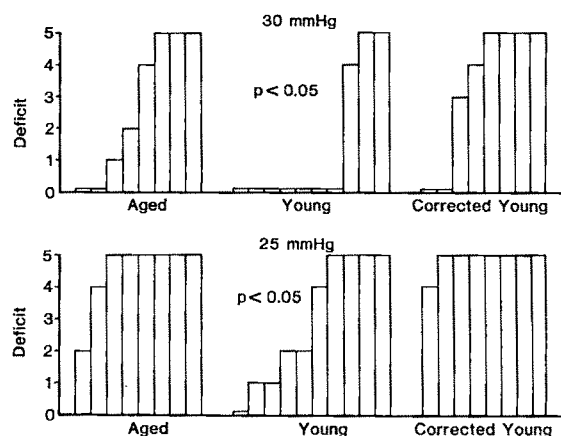
‡Young corrected = young rats with FiO₂ changed to produce Pao₂ similar to aged rats.

Figure 1. Individual neurologic deficit scores in aged, young, and Pao₂-corrected young rats after hypotension of moderate (30 mm Hg) and severe (25 mm Hg) ischemia. Deficit scores were as follows: 0 = normal, 1 = ipsilateral paw adduction, 2 = unilateral weakness with circling, 3 = stimulated seizures, 4 = unstimulated seizures, 5 = death associated with stroke.

and respiratory variables are factored out experimentally, old rats show a degree of neurologic deficit and mortality similar to that of young rats after cerebral ischemia. Blood pressure was controlled by produc-

ing the same level of hypotension during the ischemic period. Decreased alveolar gas exchange resulting in lower Pao₂ levels in old rats was compensated for by decreasing the inspired oxygen fraction in young rats to produce comparable Pao₂ levels. Using these methods we found that old rats had neurologic outcomes and neurohistopathologic changes after ischemia similar to those of young (Pao₂-corrected) rats. Regional CBF and plasma glucose levels also showed similar changes in these two groups, supporting the hypothesis that the degree of cerebral ischemia and the risk for elevation of brain lactate were similar. This suggests that neuronal viability and cerebrovascular reactivity are similar in young and in healthy aged rats during ischemia. This points to other age-related factors such as cardiovascular instability, depressed lung function, and the development of atherosclerosis as being primarily involved in the increased risk of stroke reported with aging (10,11).

The model of unilateral rat cerebral ischemia used here was adapted from the work of Mendelow et al. (12). They showed that unilateral carotid ligation

Figure 2. EEG of the right (ischemic) cerebral hemispheres of an aged and a young rat during an ischemic challenge. Baseline control EEG was recorded during 1 MAC halothane anesthesia. The 30- and 25-mm Hg EEG recordings, made after 15 minutes at each level of blood pressure, show a slowing of EEG frequency in both age groups and a decrease in amplitude in old rats. The recovery EEG was recorded 15 minutes after unclamping the carotid artery and reinfusing previously shed blood.

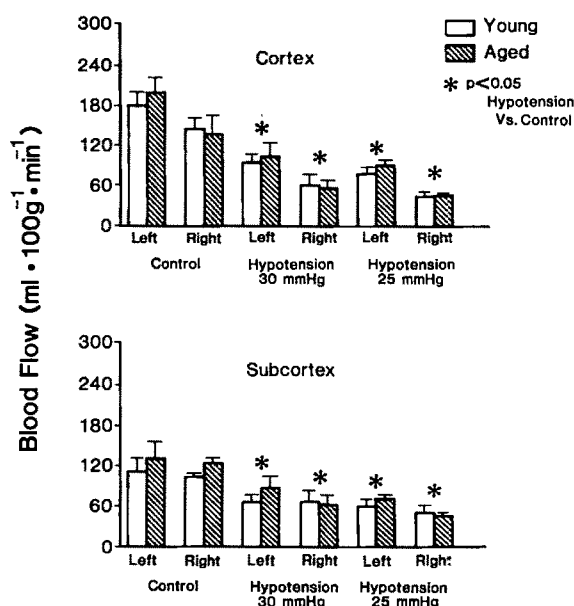
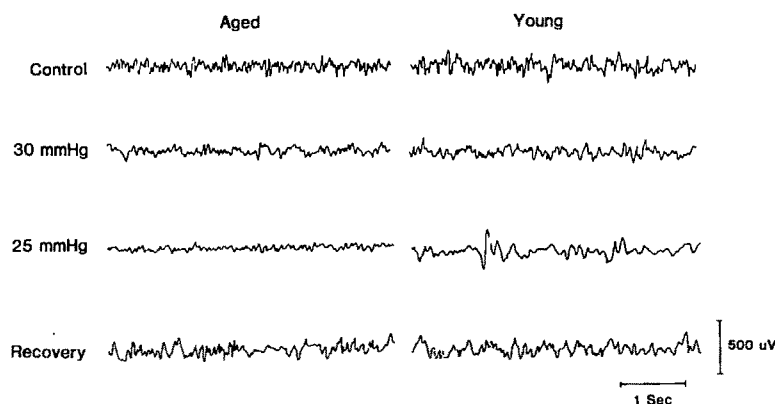


Figure 3. Right and left cortical and subcortical blood flows (CBF) during ischemia. Baseline control and hypotensive measurements made during 1 MAC halothane with the right carotid artery occluded ($n = 4$ per group). CBF decreased significantly ($*P < 0.05$) below baseline levels during hypotensive challenges. There were no significant differences in CBF between young (PaO_2 -corrected) and old rats.

combined with hypotension to 40–50 mm Hg produced a 40–50% decrease in CBF and histopathologic changes in the neocortex, striatum, and hippocampus. In an earlier study we found that 30 minutes of hypotension to levels of 25 or 30 mm Hg was required to produce both neurologic and histologic evidence of stroke (13). Data presented here show that unilateral carotid occlusion with hypotension to 25 or 30 mm Hg and inspired oxygen fractions of 0.2 and 0.3, respectively, produce graded levels of stroke-related neurologic deficits and neurohistopathologic changes. It is apparent that both the degree of hypotension and arterial oxygen content are important in determining the degree of ischemic dam-

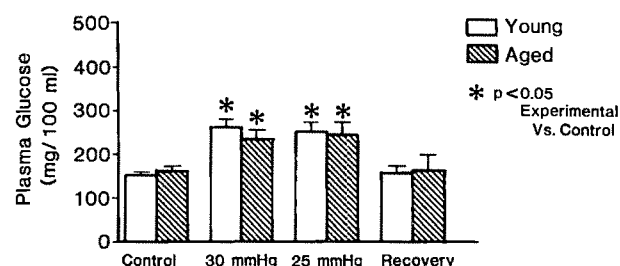


Figure 4. Plasma glucose levels during hypotension. Baseline control measurements were made during 1 MAC halothane anesthesia. The 30- and 25-mm Hg measures were made after 15 minutes at each level of blood pressure ($n = 6$ per group). The increase in plasma glucose during ischemia was similar in both age groups.

age, as evidenced by the better neurologic outcome in young rats with higher PaO_2 values. The importance of controlling these variables should be considered in models of cerebral ischemia in which blood pressure or respiratory function are not controlled (14).

Both the CBF and plasma glucose levels seen during ischemia have a potential impact on the amount of ischemic brain damage produced. The importance of CBF is obvious and was confirmed by our results showing that the right cerebral hemisphere had a lower CBF than the left hemisphere during right carotid ligation and hypotension. The fact that aged rats had CBF levels similar to those of young rats during control and ischemic challenges suggests that cerebrovascular reactivity and the ability to maintain perfusion of ischemic brain tissue shows little decrement with normal aging. This agrees with previous reports (15–17) that the cerebrovascular system of old rats shows relatively normal autoregulation and response to hypoxic and hypercapnic stimuli. Differences in cerebrovascular response between the two age groups are apparent only with extreme challenges or in pathologic stages such as chronic hypertension (17,18). The presence of cerebrovascular disease, which increases with aging in humans (11), would be expected to produce a

worse outcome in clinical episodes of ischemia. It has been reported that halothane produces brain protection in this model and that this effect may be related to the ability of halothane to depress cerebral oxygen consumption ($CMRO_2$) (13). Although $CMRO_2$ is similar in young and old rats during nitrous oxide inspiration (17), it is not known whether brain metabolism decreases to the same extent in each age group during 1 MAC halothane anesthesia. It is unlikely that there are significant differences in $CMRO_2$ depression during halothane anesthesia because MAC is corrected for a difference in anesthetic sensitivity between the two age groups.

An increase in plasma glucose levels during the ischemic period may be expected to worsen outcome by increasing brain tissue glucose concentration and lactic acid production by anaerobic metabolism (19). An elevation of brain lactate and tissue acidosis has been suggested as a primary reason for neuronal cell death in the postischemic period (20). Although the increase in plasma glucose seen in young (Pao_2 -corrected) and old rats during ischemia may have been important in increasing the degree of stroke damage, the similar levels seen in young and old rats suggest that this was not a factor for producing differences between the two age groups.

In conclusion, data presented here indicate that aged rats have outcomes similar to those of young rats in a model of unilateral cerebral ischemia. This is supported by results showing that regional CBF and plasma glucose levels are not different in young and old rats during ischemia. This indicates that cerebrovascular responsiveness and neuronal viability are not decreased in the normal aged rat during ischemia. These results do not speak to the presence of age-related factors such as cerebrovascular disease, cardiovascular instability, and compromised respiratory function, which will probably lead to a worse outcome after stroke.

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The Effect of Nail Polish on Pulse Oximetry

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COTÉ CJ, GOLDSTEIN EA, FUCHSMAN WH, HOAGLIN DC. The effect of nail polish on pulse oximetry. *Anesth Analg* 1988;67:683-6.

A randomized, blind study examined the effect of nail polish color on measurement of oxygen saturation by pulse oximetry. Fourteen adult volunteers had blue, green, purple, black, and red nail polish applied to their finger nails. A strip-chart recording of oxygen saturation (Nellcor N100) was made in room air and later interpreted in a blinded fashion. The absorption spectra of the five polishes were determined by spectrophotometry. The spectra of nine other nail polishes and three intravenous dyes also were examined. Black, blue, and green nail polish significantly lowered oximeter readings of oxygen saturation. Blue and green produced greater decreases than purple and red; black

produced an intermediate decrease. Some but not all nail polishes absorbed light at the wavelengths used by the pulse oximeter (660 nm and 940 nm). The degree of artifactual desaturation correlated best with the difference between absorbance at 660 nm and absorbance at 940 nm ($r = 0.95$). Spectrophotometric absorbance data suggest that other colors may interfere with pulse oximetry. On the basis of spectrophotometric data, brown-red nail polish was predicted to interfere with oximetry; subsequent pulse oximetry measurements confirmed the prediction. Nail polish should be removed routinely before pulse oximetry monitoring.

Key Words: OXYGEN, MEASUREMENT—oximetry. MONITORING—pulse oximetry. MEASUREMENT TECHNIQUES—pulse oximetry.

A recent report described transient but significant interference with the measurement of oxygen saturation by pulse oximetry after IV administration of indocyanine green, indigo carmine, and methylene blue dyes (1). We have observed a more nearly constant effect in thermally injured children whose fingers were stained with silver nitrate. Because emergency cases and outpatients occasionally may be anesthetized without nail polish being removed from their fingers, we questioned whether colored nail polish might also interfere with the sensor. We therefore conducted a prospective study of adult volunteers, followed by a spectrophotometric analysis of the colored nail polishes involved.

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Methods

Each volunteer had his or her nails coated with three coats of nail polish, which were allowed to dry completely between applications. To facilitate assignment of colors, the fingers were numbered from left to right (little finger of left hand = 1, and little finger of right hand = 10). Alternate fingers received one of five colors (red, blue, green, purple, and black), so that the corresponding finger of the opposite hand was not treated (control). Among the volunteers, each finger was studied at least once with each color, and the same finger was not studied repeatedly with the same color; e.g., volunteer 1, finger 1 = blue; volunteer 2, finger 2 = blue; volunteer 11, finger 1 = blue, and so on.

The sensor was applied directly to the center of the nailbed. All recordings were made on a Nellcor oximeter (N100, Nellcor Inc., Hayward, CA) with strip-chart recorder (N9000). While the volunteer breathed room air, a continuous strip-chart recording was made for each finger. These were later interpreted by an observer who was unaware of which

Table 1. Oxygenation Saturation and Absorbance Difference versus Control for Five Nail Polish Colors

Color	n	Polish	Oximeter-measured saturation (%) (Mean \pm SEM)	Range	P-value	Apparent decrease in saturation (%) (Mean \pm SEM)	Absorbance difference ($A_{660} - A_{940}$) (Mean \pm SEM)
Red	14	Yes	98.29 \pm 0.73	90-100	0.7052	0.29 \pm 0.61	0.07 \pm 0.007
	14	No	98.57 \pm 0.36	97-100			
Purple	14	Yes	96.68 \pm 0.53	93-100	0.0300	1.68 \pm 0.44	0.13 \pm 0.012
	14	No	98.34 \pm 0.34	96-100			
Black	13	Yes	95.30 \pm 1.29	86-100	0.0003*	3.08 \pm 0.96	0.14 \pm 0.002
	14	No	98.50 \pm 0.44	95-100			
Green	13	Yes	93.35 \pm 0.89	89-98	<0.0001*,†	5.19 \pm 0.84	0.43 \pm 0.03
	14	No	98.64 \pm 0.39	96-100			
Blue	12	Yes	92.75 \pm 1.21	85-98	<0.0001*,†	5.92 \pm 1.08	0.48 \pm 0.03
	14	No	98.64 \pm 0.37	97-100			

*Significantly different from control.

†Significantly different from purple and red.

subject was studied and what color nail polish, if any, had been applied. A recording was considered adequate only when the recorded heart rate was constant, indicating that the detector was sensing arterial pulsation. In four instances, all of which involved polished nails (one green, two blue, and one black), no reading could be obtained; these were treated as missing values in the data analysis.

Absorption spectra of nail polishes were obtained on samples single-coated onto microscope cover glasses. Each coated cover glass was taped across the light beam entry port on an integrating sphere placed in the sample chamber of a spectrophotometer (Cary 17, Varian, Palo Alto, CA). An uncoated cover glass was taped across the light beam entry port on an integrating sphere placed in the reference compartment. Absorption spectra were recorded from 600 to 1000 nm. The difference in absorbance at 660 and 940 nm, corrected for absorbance by the blank, was recorded for each study. Spectra of the blue and green nail polishes were replicated ten times because the recorded absorbance appeared to exhibit some scatter; spectra of black, red, and purple nail polishes were replicated five times. Absorption spectra were recorded for single samples of clear and nine other shades of nail polish (brown, brown-red, gray, lime, orange, pink, red-purple, vanilla white, and yellow).

Brown-red nail polish had an absorbance difference that was intermediate between the absorbance differences of most other colors and the absorbance differences of blue and green nail polishes. Therefore, we carried out further recordings on brown-red polish to establish its absorbance difference more precisely, and we undertook a second pulse oximetry study of five volunteers. Additionally we examined the absorbance spectra of three intravenous dyes (indigo carmine 0.8%, indocyanine green 0.25%, and

methylene blue 1.0%), diluted 1000 times in 0.9% saline under experimental conditions similar to those in a previous report (1).

Statistical analysis of the data focused on the difference in oxygen saturation between the fingers to which nail polish had been applied and the corresponding unpolished fingers of the subject's other hand. To allow for variation among subjects, we used analysis of variance, with color and subject as factors. We judged the significance of differences according to Bonferroni *t*-tests, using a simultaneous significance level of 0.05. Each of the 15 comparisons (5 color vs control and 10 pairwise comparisons among colors) was considered significant if its *P* value was $<0.05/15 = 0.0033$ (2). Spectrophotometric data were summarized by mean and SEM; the correlation coefficient was used to summarize the relation between percentage decrement in oximeter reading and absorbance difference.

Results

Fourteen subjects were studied; the age (mean \pm SD) was 29.0 ± 9.2 years. Black, blue, and green, but not red or purple nail polish produced significant decreases in oxygen saturation readings compared with the unpolished control (Table 1). Comparison of results by color found that blue and green nail polish resulted in significantly lower oxygen saturation readings than did purple and red nail polish. Black nail polish produced an intermediate degree of sensor interference resulting in a significant reduction in oxygen saturation readings compared with the unpolished control. Black, however, in pairwise comparisons did not differ significantly from any of the four other colors.

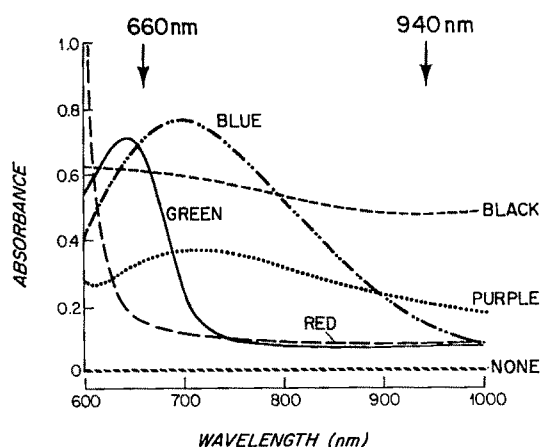


Figure 1. Absorption spectra for the five nail polish colors studied. Blue, green, and black have high absorption at one or both wavelengths measured by the pulse oximeter (vertical arrows). The absorption for black is similar at both wavelengths measured by the oximeter.

Some but not all of the nail polishes demonstrated absorbance at the same wavelengths used by the oximeter sensor (660 and 940 nm). Figure 1 presents examples of the absorption spectra for the five nail polish colors used in the clinical study. Apparent decreases in oxygen saturation did not correlate as strongly with nail polish absorbance at 660 nm ($r = 0.84$, $P = 0.072$) or at 940 nm ($r = 0.23$, $P = 0.71$) as with the absorbance difference between 660 and 940 nm ($r = 0.95$, $P = 0.012$) (Fig. 2). For example, green nail polish produced larger apparent decreases in oxygen saturation than black nail polish, even though the absorbances at both 660 and 940 nm were greater for black than for green. However, the absorbance difference ($A_{660} - A_{940}$) was greater for green than for black nail polish (Fig. 1). Differences in absorbance for the clear polish and the nine other colors determined once each were: clear 0.00, gray 0.11, yellow 0.09, lime 0.17, brown-red 0.36, brown 0.16, orange 0.06, vanilla white 0.01, pink 0.07, and red-purple 0.01.

Examination of oximetry recordings with the brown-red nail polish resulted in a mean (\pm SEM) saturation of 97 ± 0.45 vs $99 \pm 0.32\%$ for unpolished controls; the mean absorbance difference ($A_{660} - A_{940}$), based on five determinations, was 0.288 ± 0.015 . The absorbances at 660 nm for the intravenous dyes were similar to those previously reported. The absorbances at 940 nm, not previously reported, were negligible for all three dyes.

The absorbance studies were carried out at 660 and 940 nm because the sensors used in our clinical study functioned at these wavelengths; newer sensors function at 660 and 920 nm. Differences in absorbance

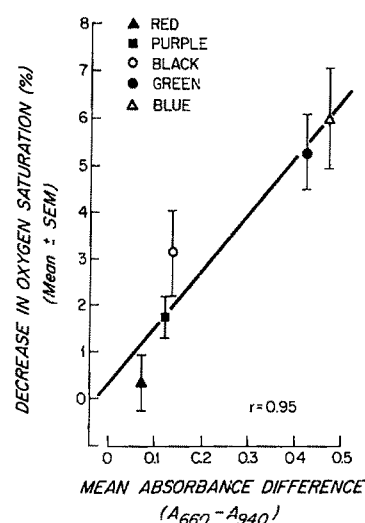


Figure 2. Mean decrease in saturation vs mean absorbance difference. Note the apparent linear relation.

between 920 and 940 nm are not likely to alter our conclusions (Fig. 1).

Discussion

Many factors influence the accuracy of pulse oximetry. These include movement and compression of the sensor, hemoglobinopathy, severe desaturation, inadequate perfusion, electrocautery, infrared heating lights, and intravenously injected dyes (1,3,4). Our study demonstrates that nail polish significantly alters the accuracy of pulse oximetry readings if the oximeter sensor is applied directly over the nailbed and if the polish absorbs light differentially at the wavelengths transmitted and absorbed by the photodetector of the oximeter (660 and 940 nm, Nellcor). In some situations nail polish may make it impossible to obtain any recording, as demonstrated in four subjects with three different colors in this study (green, blue, black). Because the pulse oximeter functions by examining the difference in absorbance at two wavelengths, any factor that increases the difference in absorbance between 660 and 940 nm will cause the oximeter to falsely indicate desaturation. Both green and blue nail polish demonstrated increased absorbance at 660 compared to 940 nm and thus "tricked" the sensor into indicating desaturation. Black, on the other hand, has great absorbance at both 660 and 940 nm, but the difference in absorbance between 660 and 940 nm is less than that produced by green or blue, so that black produced less apparent desaturation. Kataria and Lampkins (5) reported no interference caused by nail polish but did not specify the color(s). We assume that their study did not include black,

green, or blue nail polish. Because red nail polish is most frequently used, it is likely that they examined red nail polish; if so, our observation that red nail polish caused no interference agrees with their report. Unlike nail polishes, all three intravenous dyes previously studied exhibited zero absorbance at 940 nm, thereby permitting correlations between oximeter errors and absorbance at 660 nm (1).

The most important implication of the correlation between oximetry interference and absorbance differences is that visible color is not necessarily a good predictor of oximetry interference. It is conceivable that some red pigments might absorb strongly near the infrared region of the spectrum, creating large negative absorbance differences and thus large oximeter errors. It is also possible that some black, blue, and green pigments might absorb equally in the red and near-infrared portions of the spectrum, creating small absorbance differences and thus no interference with oximetry. The spectra of the additional nine nail polish colors that we examined by spectrophotometry suggested that several of these colors (brown-red, brown, lime) are likely to interfere with the oximeter. Color alone might suggest that brown-red, like red nail polish, would cause no interference. Brown-red, however, demonstrated absorbance differences well within the range of absorbance differences observed

for green nail polish; a mean 2% decrease in apparent saturation was found.

We have presented evidence that blue, green, and possibly black and brown-red nail polishes interfere with pulse oximetry. We have reported spectrophotometric evidence that other colors such as brown and lime may interfere with pulse oximetry. It is impractical to test all variations in color and pigment composition in commercial nail polishes. Therefore, the present study emphasizes the necessity to remove all nail polish before application of an oximeter sensor to prevent erroneous oximeter readings.

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Effects on Gastric Emptying of Thoracic Epidural Analgesia with Morphine or Bupivacaine

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THORÉN T, WATTWIL M. Effects on gastric emptying of thoracic epidural analgesia with morphine or bupivacaine. *Anesth Analg* 1988;67:687-94.

The effects of thoracic epidural analgesia on gastric emptying were evaluated in healthy fasting volunteers. In ten volunteers, 4 mg of epidural morphine were injected at the T4 level, and ten volunteers received thoracic epidural analgesia with 0.5% bupivacaine, the latter causing block of the sympathetic innervation to the stomach. Acetaminophen absorption was used as an indirect measure of the rate of gastric emptying. After establishment of the analgesia with bupivacaine, or 160 (110-185) minutes after the administration of epidural morphine, 1.5 g acetaminophen dissolved in water was ingested. Serum samples were taken at 15-minute intervals for 2 hours and serum acetaminophen concentrations were determined by an immunologic method. Control acetaminophen absorption studies without thoracic epidural analgesia were performed in all 20 subjects on another occasion. During epidural analgesia with mor-

phine mean serum acetaminophen concentrations were lower ($P < 0.05$), the maximum serum acetaminophen concentration was lower ($P < 0.01$), the time taken to reach the maximum concentration was longer ($P < 0.02$), and the area under the concentration time curve from 0 to 60 minutes was smaller ($P < 0.01$) than in the control study. The corresponding values during epidural analgesia with bupivacaine did not differ from the control values. Four subjects with extremely delayed gastric emptying during epidural analgesia with morphine showed no delay in gastric emptying after receiving 4 mg morphine intramuscularly. Serum morphine concentrations were lower after epidural than after intramuscular morphine. In summary, 4 mg epidural morphine delayed gastric emptying. This was not a systemic effect of morphine. Thoracic epidural analgesia with bupivacaine had no influence on gastric emptying.

Key Words: ANESTHESIA, EPIDURAL—bupivacaine, morphine. GASTROINTESTINAL TRACT—gastric emptying.

Epidural analgesia, with both local anesthetics and opioids, is an increasingly popular method of providing pain relief. However, little is known of the effects of this treatment on gastric emptying. One major side effect of systemically administered opioids is a delay in gastric emptying (1). The question whether epidural morphine influences gastric emptying does not appear to have been investigated. It has been suggested that, normally, gastric emptying is under some degree of adrenergic inhibi-

tion, because it is accelerated by β -adrenoceptor antagonists (2). Stimulation of the sympathetic nervous system by pain delays gastric emptying (3). To our knowledge there have been no investigations of gastric emptying in which the sympathetic innervation to the stomach (T6-T10) has been blocked by epidural analgesia. Acetaminophen is not absorbed from the stomach but is rapidly absorbed from the upper small intestine after passing through the pylorus (4,5). Therefore acetaminophen absorption can be used as a measure of gastric emptying (4,6).

The aim of the present study was to evaluate the effects of epidural analgesia on gastric emptying in healthy volunteers. Both epidural analgesia with morphine and epidural analgesia with a local anesthetic causing block of the sympathetic innervation to the stomach (T6-T10) were studied. The acetaminophen absorption method was used for studying gastric emptying (4,6).

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Materials and Methods

Twenty healthy volunteers, 18 men and two women, took part in the study. None were taking any medication and none had a history of gastrointestinal symptoms. The study was approved by the Ethics Committee of the Örebro County Council. The subjects received both verbal and written information and gave written consent to participation. They were randomly classified into two groups, one (10 men, 32.2 ± 5.0 years old, weight 73.1 ± 9.0 kg, height 180.5 ± 5.1 cm; values in mean \pm SD) being given epidural morphine, the other (8 men and 2 women, 33.6 ± 4.7 years old, weight 72.9 ± 9.1 kg, height 177.3 ± 8.3 cm) epidural bupivacaine.

The epidural space at the level of T4 was identified by the "hanging-drop" technique, using the paramedian approach. An epidural catheter was inserted 2-3 cm into the epidural space.

Acetaminophen Absorption Study

With the subject in a half-sitting position, 1.5 g of acetaminophen suspension was taken orally within 1 minute. This suspension was prepared before each study by dissolving three Alvedon (Astra Läkemedel AB, Södertälje, Sweden) effervescent tablets in 200 ml water (at room temperature). The suspension was not effervescent when administered. After having taken the acetaminophen suspension, the subject lay supine throughout the study period. Venous blood samples were obtained through an indwelling cannula at 15-minute intervals for 2 hours after the administration of acetaminophen. The serum was stored at -20°C pending measurement of its acetaminophen concentration, which was performed by an immunologic method including fluorescence polarization (TDx Acetaminophen, Abbot Laboratories, North Chicago). Acetaminophen concentration was expressed as $\mu\text{mol/L}$ ($1.00 \mu\text{mol/L} = 0.15 \mu\text{g/ml}$). Acetaminophen concentration curves were produced, and the mean maximum acetaminophen concentration (C_{max}), the mean time taken to reach the maximum concentration (t_{max}), and the area under the serum acetaminophen concentration time curve from 0 to 60 min were calculated. T_{max} was assumed to be 120 minutes if no acetaminophen was detected in any sample during the study period.

Morphine Analysis

Morphine concentrations in serum samples were determined by gas chromatography with electron-capture detection (7).

Procedure

The study started in the morning, when the subjects had been fasting for at least 8 hours. A continuous infusion of acetated Ringer's solution was given at a rate of 60 ml/hr throughout the study. In addition, 500 ml of the acetated Ringer's solution was given over a period of 30 minutes just before the epidural block.

The subjects given epidural morphine received 4 mg morphine (volume 10 ml) by the epidural route 160 (110-185) minutes before the acetaminophen absorption study. In the epidural bupivacaine group, 0.5% bupivacaine was given in sufficient amounts to achieve and maintain a sensory block (pinprick) including at least dermatomes T6-T10 throughout the acetaminophen absorption study. The latter study was begun 104 (80-120) minutes after the first bupivacaine injection and at that time some of the subjects had received additional bupivacaine. The times at which blood samples were obtained for acetaminophen assays were the same in both groups of volunteers based on the time at which the acetaminophen was administered orally, but the times differ when referred back to the time at which epidural morphine or epidural bupivacaine were administered. Control acetaminophen absorption studies without thoracic epidural analgesia were performed in each of the same subjects at least 5 days before or after the other studies.

In four subjects given epidural morphine, acetaminophen was either not detected in the serum until 90 minutes after the administration of acetaminophen, or not detected at all. A further study was therefore performed in these four subjects on another occasion after an IM injection of 4 mg morphine (volume 0.4 ml), i.e. the same dose as in the epidural study. The acetaminophen absorption was studied in exactly the same way after intramuscular as after epidural morphine. Serum samples for morphine concentration determinations were taken just before the acetaminophen was given in these four subjects, and at a corresponding time in five subjects after epidural administration of morphine. In three of these subjects the morphine concentration was determined after both intramuscular and epidural administration of morphine.

Statistics

Student's *t*-tests for paired and unpaired samples were used for statistical analysis of the results, which are presented as means \pm SEM. $P < 0.05$ was considered statistically significant.

Figure 1. Serum acetaminophen concentrations in the epidural morphine group at different times after ingestion of acetaminophen, compared with the control values. * $P < 0.05$; ** $P < 0.01$.

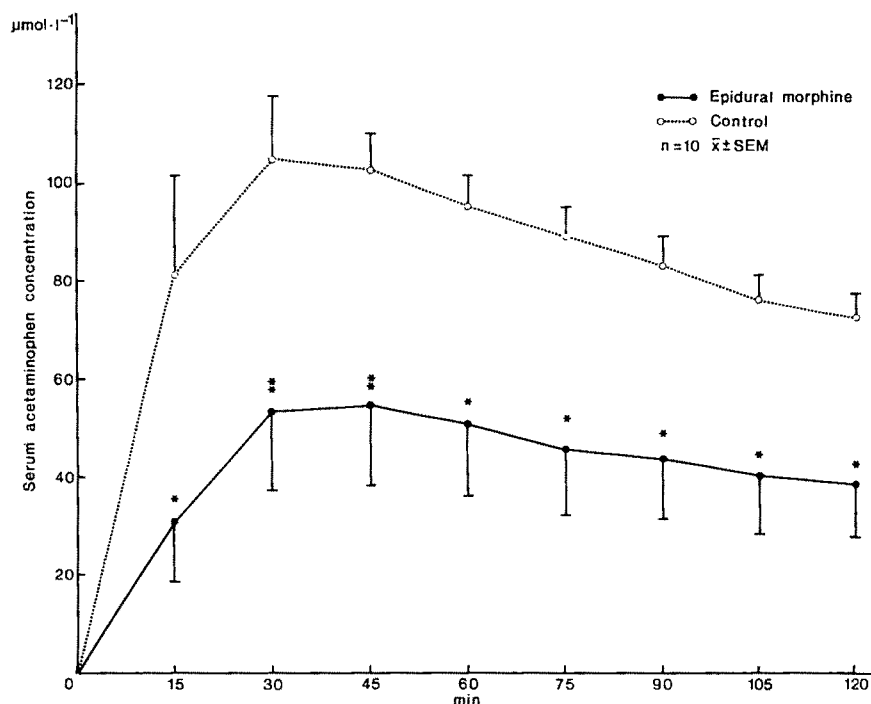


Table 1. Area Under the Serum Acetaminophen Concentration Time Curve*

	Control	P-Value	TEA
Epidural morphine group (n = 10)	4,617 ± 25	< 0.01	2,425 ± 745
Epidural bupivacaine group (n = 10)	5,669 ± 622	NS	5,152 ± 525

*From 0 to 60 minutes in $\mu\text{mol}\cdot\text{L}^{-1}\cdot\text{min}$.

Values are means \pm SEM.

Abbreviations: TEA, thoracic epidural analgesia; NS, not significant.

Results

Effects of Epidural Morphine

Epidural morphine significantly delayed the acetaminophen absorption. Serum acetaminophen concentrations were significantly lower and the area under the curve from 0 to 60 minutes was significantly less than the corresponding control values (Fig. 1, Table 1). The maximum serum acetaminophen concentrations averaged $60.8 \pm 17.2 \mu\text{mol/L}$ during epidural analgesia with morphine and $125.0 \pm 11.4 \mu\text{mol/L}$ in the control study. This difference was statistically significant. The times taken to reach C_{max} averaged 73.5 ± 13.3 and 36.0 ± 5.1 minutes in these two situations, respectively. This difference was also statistically significant.

In four subjects in the epidural morphine group no acetaminophen was found in the serum until 90 minutes after the acetaminophen administration (Fig.

2). Even when these subjects were excluded, the remaining six subjects in this group had lower mean serum acetaminophen concentrations during epidural analgesia with morphine than in the control study, but the values were not significantly lower until 90 minutes after acetaminophen ingestion (Fig. 3).

Four of the ten subjects in the epidural morphine group experienced nausea, which began 2–5 hours after the administration of morphine and lasted for up to 23 hours. The same four subjects had the greatest delay in acetaminophen absorption. One subject had nausea before but not during the acetaminophen absorption study, the other three subjects complained of nausea after the acetaminophen absorption study was completed. One of these subjects vomited several times after the study. Six of ten subjects given 4 mg epidural morphine complained of itching, which started 2–8 hours after the morphine administration and which lasted from 1 hour and 40 minutes to 24 hours.

Effects of Intramuscular Morphine

After the intramuscular injection of 4 mg morphine the serum acetaminophen concentrations, C_{max} and t_{max} did not differ from the corresponding control values (Figs. 2 and 4). Compared with the findings after administration of epidural morphine, serum acetaminophen concentrations after intramuscular

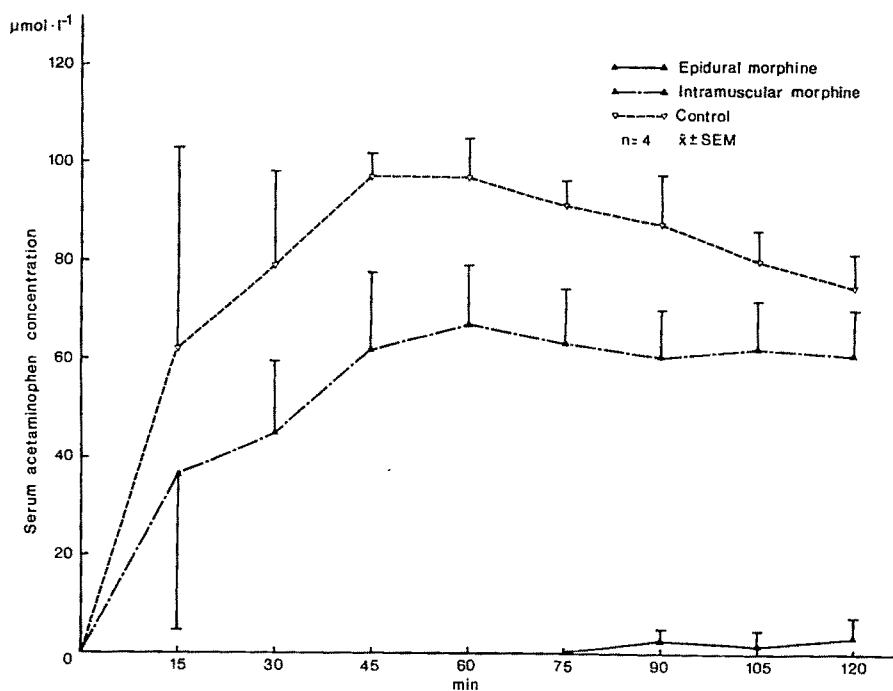


Figure 2. Serum acetaminophen concentrations at different times after ingestion of acetaminophen in four subjects after epidural or intramuscular administration of morphine, compared with the control values.

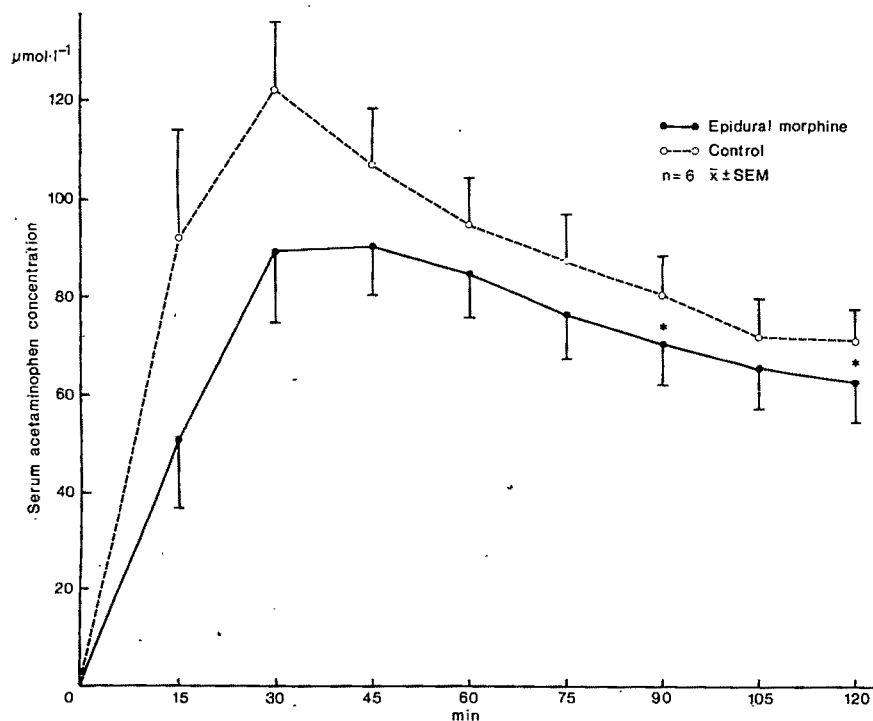


Figure 3. Serum acetaminophen concentrations at different times after ingestion of acetaminophen in six subjects who had received epidural morphine, compared with the control values. * $P < 0.05$.

morphine injection were significantly greater 45 minutes after ingestion of acetaminophen and onward (Fig. 2). C_{max} was higher and t_{max} shorter after intramuscular injection of morphine than during epidural morphine analgesia (Fig. 4). None of the subjects given 4 mg morphine intramuscularly complained of nausea or itching.

Morphine Concentrations After Intramuscular and Epidural Morphine

Just before the acetaminophen absorption study, which was performed 110–185 minutes after epidural or intramuscular administration of morphine, the serum morphine concentration was 1.28 ± 0.16 ng/ml

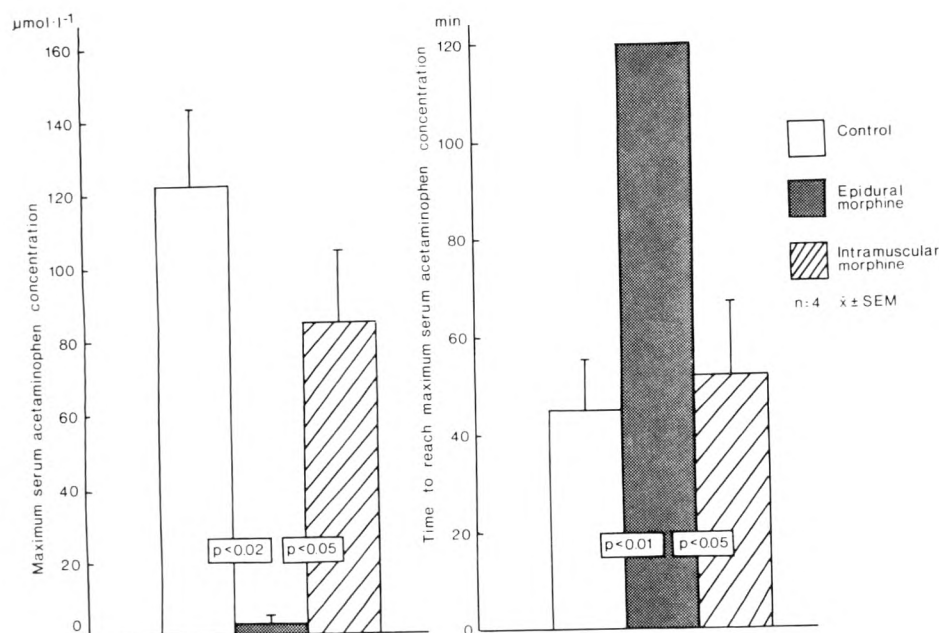


Figure 4. Maximum serum acetaminophen concentration and time taken to reach this maximum in four subjects after epidural or intramuscular administration of morphine, compared with the control values.

in subjects given epidural morphine ($n = 5$) and 2.4 ± 0.14 ng/ml in those given morphine intramuscularly ($n = 4$; Table 2). In the three volunteers in whom serum morphine concentrations were determined both after intramuscularly administered and after epidural morphine, the morphine concentrations were lower after epidural than after intramuscular administration (Table 2). Statistical analyses were not performed in these three subjects because of the small number.

Effects of Epidural Bupivacaine

In the bupivacaine epidural group the serum acetaminophen concentrations and the area under the curve during the analgesia did not differ from control values (Fig. 5, Table 1). Neither were there any significant differences in C_{max} or t_{max} .

The extent of the sensory blockade after thoracic epidural analgesia with bupivacaine varied between C6-T1 and T10-L1. All subjects given epidural bupivacaine had sensory blockade within the dermatomes T6-T10 during the acetaminophen absorption study. They received 16.4 (13-20) ml of 0.5% bupivacaine. Bilateral Horner's syndrome occurred in nine of the ten subjects.

Differences Between the Epidural Morphine and Epidural Bupivacaine Groups

The serum acetaminophen concentrations during thoracic epidural analgesia with morphine were signifi-

cantly lower than those during thoracic epidural analgesia with bupivacaine (Figs. 1 and 5). C_{max} , t_{max} and the area under the curve also differed between the two groups (Figs. 1 and 5, Table 1).

There were no differences in serum acetaminophen concentrations, C_{max} , t_{max} , or the areas under the curves between the two control groups (Figs. 1 and 5, Table 1).

Discussion

In this study of healthy volunteers, high thoracic epidural analgesia with morphine resulted in greatly retarded absorption of orally administered acetaminophen, expressed as a low C_{max} , a long t_{max} , and a small area under the serum acetaminophen concentration time curve. This must have been caused by a delay in gastric emptying. Acetaminophen is rapidly absorbed from the upper small intestine but is not absorbed from the stomach (4,5). The rate of gastric emptying therefore determines the rate of absorption of orally administered acetaminophen (4,5,8,9). In investigations in which a radioisotopic method and acetaminophen absorption have been compared as methods for measuring gastric emptying, a good correlation between the two methods has been found (4,6).

Therapeutic doses of parenteral opioids delay gastric emptying for up to 5 hours (10,11) probably in a dose-dependent way (1). To investigate whether 4 mg epidural morphine has a systemic effect on gastric emptying, four subjects in whom gastric emptying

Table 2. Serum Morphine Concentrations in Six Volunteers after IM or Epidural Administration of 4 mg Morphine

Age (yrs)	Weight (kg)	Height (cm)	Morphine concentration (ng/ml) after		Minutes after morphine administration
			Intramuscular morphine	Epidural morphine	
30	77	181	2.2	0.8	155
25	72	186	2.3	1.0	185
35	62	173	2.3	1.4	110
29	60	173	2.8	—	140
33	71	180	—	1.6	170
43	65	180	—	1.6	170

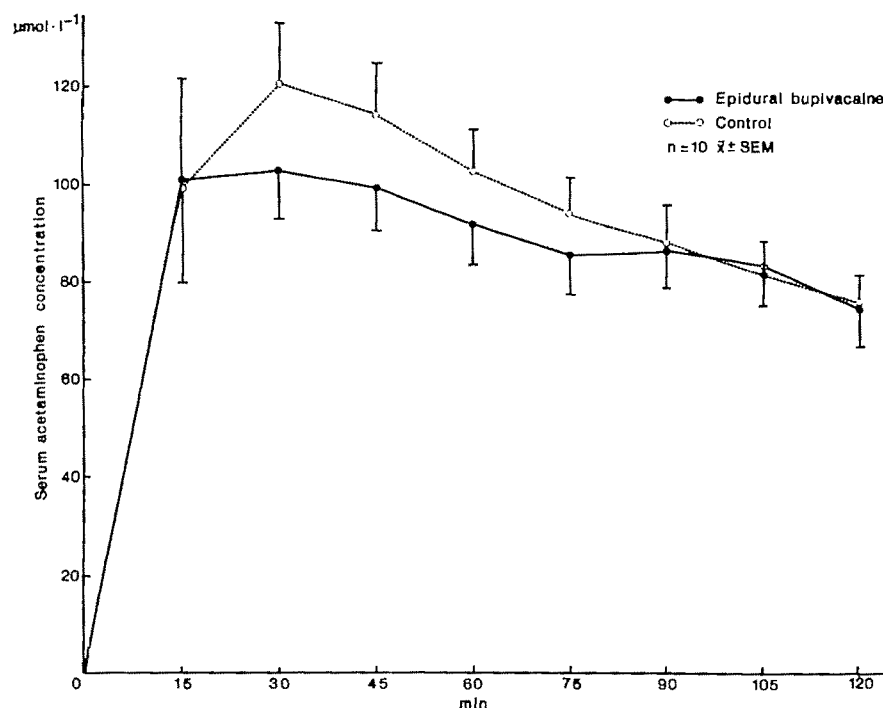


Figure 5. Serum acetaminophen concentrations in the epidural bupivacaine group at different times after ingestion of acetaminophen, compared with the control values. There are no statistical significant differences.

was greatly delayed during epidural morphine analgesia were given 4 mg morphine intramuscularly. The serum concentrations of morphine were low irrespective of the mode of administration, but they were lower after epidural than after intramuscular administration of morphine. Acetaminophen absorption and thus gastric emptying were not delayed at these low morphine concentrations when the morphine had been injected intramuscularly. These results thus indicate that epidural morphine delays gastric emptying independent of its systemic effects. Therefore it is evident that there exists an opioid-sensitive structure in the central nervous system influencing gastrointestinal motility. This is in accordance with results of a study in which the analgesic effects of intramuscular and epidural morphine on postoperative pain after gastropasty were compared, when the volume of gastric aspirate was found to be greater in patients receiving epidural morphine (12).

In our study subjects with extremely delayed gastric emptying suffered from pronounced nausea, but the nausea started after the acetaminophen absorption study, suggesting that the nausea itself was not the precause of the delay in gastric emptying.

In previous studies in which lumbar epidural analgesia with local anesthetics was given for postoperative pain relief the day after abdominal hysterectomy, a moderate delay in gastric emptying was observed (13). However, gastric emptying was not affected during lumbar epidural analgesia after minor surgery on the lower extremities (14). In those clinical investigations on gastric emptying, lumbar epidural analgesia with local anesthetics was used for pain relief (13-15). Consequently the afferent input was blocked. In a study by Gelman et al. (16), it was found that high thoracic epidural anesthesia with bupivacaine increased gastric electric activity after upper abdominal surgery, but in that study gastric empty-

ing was not measured. In the present study gastric emptying was measured during blockade of the efferent sympathetic innervation to the stomach and without other interacting factors such as surgical trauma or drugs. The epidural anesthesia was more extended than necessary for blocking the innervation to the stomach. The reason was that the present investigation was preceded by an esophageal motility study (17).

Stimulation of the adrenergic nerves inhibits the activity of cholinergic excitatory neurons and hence the motility of the gastrointestinal tract (18-21). β -Adrenoceptor antagonists increase gastric emptying in healthy volunteers (2). This suggests that under normal conditions the stomach is under some degree of adrenergic inhibition (2). Other authors have claimed that in the resting individual there is probably no tonic activity of the adrenergic nerves that go to the intrinsic ganglia of the gastrointestinal tract (20). This explains why thoracic epidural analgesia with bupivacaine did not affect the gastric emptying in the present study. Thus, if there is only weak sympathetic discharge, sympathetic blockade will add nothing significant to the nervous control of gastric emptying (16). Complete sympathetic block may be difficult to achieve (22,23), but in nine of our ten subjects, thoracic epidural analgesia with 0.5% bupivacaine resulted in bilateral Horner's syndrome, indicating total thoracic sympathetic block. Gastric emptying is dependent not only on the gastric motility but also on the coordination of the contractile activity of the stomach and duodenum. A number of factors modify gastric emptying. The main ones are the physicochemical properties of a meal and the neural and hormonal control (24). The vagal and sympathetic innervation of the stomach coordinates and controls the smooth muscle and enteric nervous system (25,26). It is therefore clear that numerous other factors apart from sympathetic activity play a role in regulating gastric emptying. However, the present study was standardized and was not associated with surgical trauma.

Abdominal operations result in inhibition of gastrointestinal motility through reflex activation of both vagal nonadrenergic, noncholinergic and sympathoadrenergic efferent inhibitory pathways (21). Spinal and splanchnic anesthesia attenuate this depressive effect on gastrointestinal motility (21,27-29). Epidural anesthesia normalizes the electric activity of the stomach and intestine after cholecystectomy (16). This suggests that in a situation with considerable sympathetic discharge, thoracic epidural analgesia with bupivacaine may diminish the suppression of gastric emptying.

High thoracic epidural analgesia with morphine delays gastric emptying, as shown in the present study. This delay results in an increased volume of gastric contents, which presumably predisposes to nausea and vomiting and makes reinstitution of oral feeding difficult. Care must be taken to avoid aspiration on induction of anesthesia and in the very sick patient. If drugs are given orally, their absorption is delayed (6,9,30) and erratic (5), because most drugs are not absorbed to any significant extent in the stomach (5,9). When epidural morphine stops delaying gastric emptying, there is a risk that a large amount of previously orally administered drugs will suddenly be transported to the intestine and absorbed, possibly resulting in overdose or toxic effects (6). The question as to whether epidural morphine administered in the lumbar region, and epidural morphine used for a prolonged period, cause delayed gastric emptying has not yet been answered and needs further investigation.

In summary, epidural morphine given at the T4 level significantly delayed gastric emptying in healthy volunteers. This was not a systemic effect of the morphine. High thoracic epidural analgesia with bupivacaine did not influence gastric emptying.

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Clinical Reports

Does Nitrous Oxide Cause Regional Wall Motion Abnormalities in Patients with Coronary Artery Disease?

An Evaluation by Two-Dimensional Transesophageal Echocardiography

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Key Words: ANESTHETICS—gases. HEART, MYOCARDIUM—abnormal motion.

Nitrous oxide has enjoyed widespread use as a supplement to narcotic-based anesthetics. Previously available data on the cardiovascular effects of nitrous oxide–narcotic interaction have been contradictory (1,2). Nitrous oxide does not consistently depress global left ventricular function in patients with coronary artery disease (1). Similarly, in a canine model of acute coronary stenosis, nitrous oxide caused no global deterioration of left ventricular function. However, regional dysfunction was observed in the territory supplied by the critically constricted coronary artery (2). To determine if nitrous oxide causes acute regional wall motion abnormalities consistent with ischemia, we studied seven patients with coronary artery disease undergoing aortocoronary bypass grafting with quantitative two-dimensional transesophageal echocardiography (2D-TEE), as well as hemodynamic measurements during the precardiopulmonary bypass period.

Patients and Methods

Seven patients ($n = 7$) with symptomatic coronary artery disease were selected for study. All patients

were receiving nitrates and β -blocking agents. Four of the seven were also maintained on calcium entry blockers, and two of the seven were taking diuretics.

Following a Human Investigation Committee-approved protocol, and with informed consent, these patients were anesthetized with sufentanil (20 $\mu\text{g}/\text{kg}$)–oxygen ($\text{FIO}_2 = 1.0$). Muscle relaxation was achieved with pancuronium (0.1 mg/kg). After tracheal intubation, a two-dimensional transesophageal phased array echoprobe (Diasonics) mounted on a gastroscope was positioned in the esophagus. A stable, short-axis view of the left ventricle was obtained at mid-papillary muscle level. Images were displayed on a Varian 3400R echocardiography system and recorded on VHS-format videotape for subsequent playback and computer-aided analysis.

After sternotomy, and after a control period of ventilation with 100% oxygen, patients were randomized to alternating 10-minute sequences of 70% nitrous oxide in oxygen and 70% nitrogen in oxygen. This was followed by a final 10-minute period of ventilation with 100% oxygen. Total fresh gas flow was 10 L/min. Ten minutes were allowed in each period to reach a steady state. Data were collected at the end of each of the four measurement periods, including the following measurements made at end-exhalation: heart rate (HR), mean blood pressure (BP), mean right atrial pressure (RAP), mean pulmonary artery pressure (PA), mean pulmonary capillary wedge pressure (PCWP), cardiac output (CO) in duplicate, and echocardiographic images as well as ECG leads II and V₅. Arterial and mixed venous blood gases were also measured. The following derived variables of cardiovascular performance were

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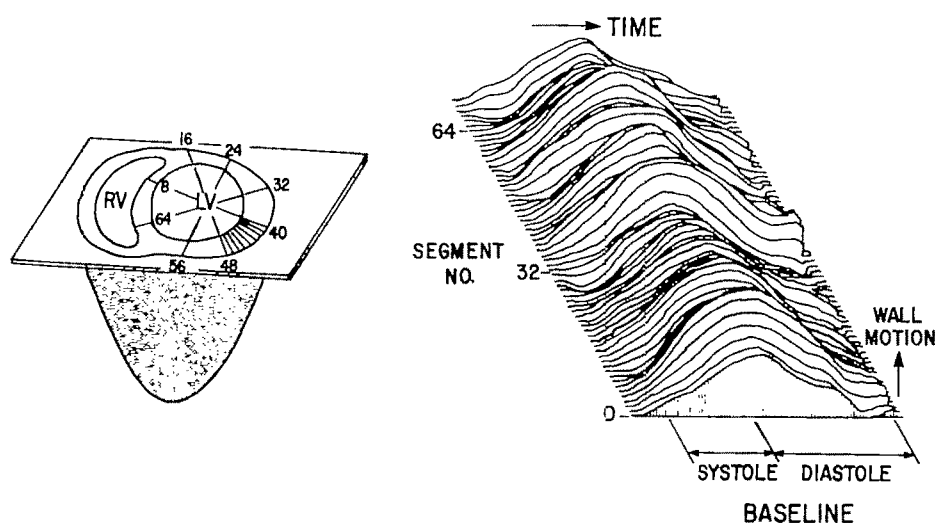


Figure 1. Computer analysis of wall motion is generated from the two-dimensional transesophageal echocardiographic cross-section of the left ventricle. Each of sixty-four equiangular segments is analyzed for wall motion during systole and diastole.

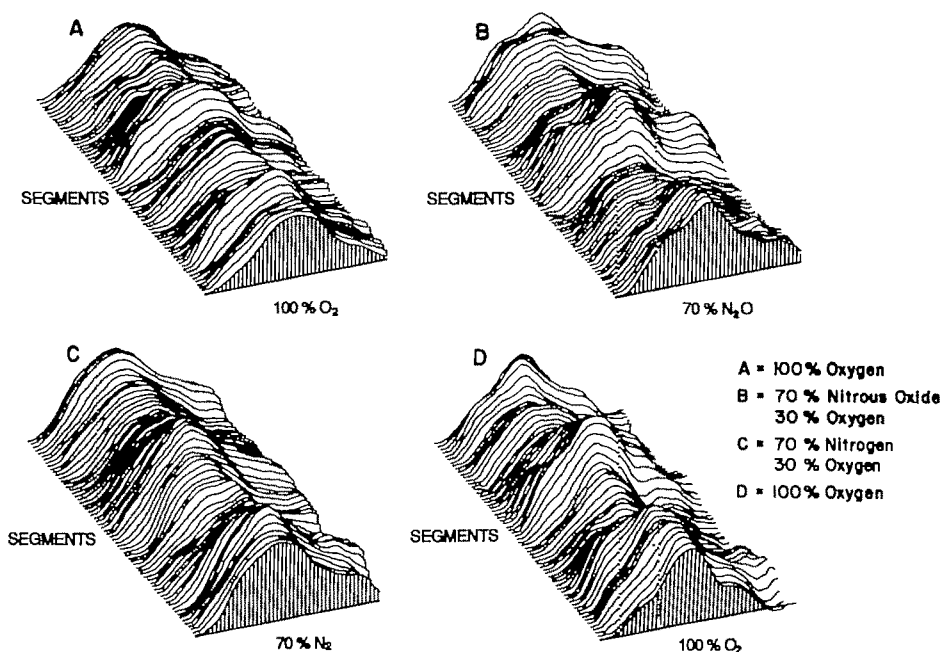


Figure 2. A representative example from a single patient of the computer-generated wall motion data during the four study periods.

calculated using standard formulas: cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), pulmonary vascular resistance index (PVRI), left ventricular stroke work index (LVSWI), right ventricular stroke work index (RVSWI), coronary perfusion pressure (CPP), and arterial oxygen content (CaO_2) (3). Serial ECGs and creatine phosphokinase determinations were conducted postoperatively.

Video images were digitized and analyzed on a Franklin 1200 echocardiography analysis system employing an edge detection algorithm. The peak of the R wave was used to select the video frame that represented end-diastole, and the video frame with the

smallest left ventricular cavity area was chosen to represent end-systole. Each left ventricular cross-section was divided into 64 equiangular segments to facilitate regional wall motion analysis. Correction for translational and rotational motion was achieved using a floating-axis center-of-mass reference system (4). A typical computer-aided analysis of a cardiac cycle is illustrated in Figure 1. Inward motion, systole, is represented by a rise in the contour. Outward motion, which may represent either diastole or paradoxical wall motion, is represented by a fall in the contour. Figure 2 illustrates the results from the four periods of the study for a representative patient. Ejection fraction area (EF_{AREA}) is defined as (ED_{AREA}

Table 1. Hemodynamic Performance*

	100% O ₂	70% N ₂ O/O ₂	70% N ₂ /O ₂	100% O ₂
HR (beats/min)	68 ± 4	65 ± 3	70 ± 4	70 ± 4
BP (mm Hg)	87 ± 5	78 ± 4	87 ± 6	85 ± 8
PA (mm Hg)	18 ± 4	18 ± 2	19 ± 2	16 ± 2
PCWP (mm Hg)	11 ± 2	11 ± 2	10 ± 2	9 ± 2
RAP (mm Hg)	8 ± 2	7 ± 2	7 ± 2	6 ± 2
CPP (mm Hg)	48 ± 3	46 ± 4	49 ± 4	52 ± 6
CO (L/min)	5.1 ± 0.4	4.2 ± 0.3	4.7 ± 0.3	4.3 ± 0.3
PaO ₂ (mm Hg)	465 ± 26	130 ± 12†	99 ± 9†	378 ± 22†

*Mean ± SEM.

†P < 0.05 when compared to the first 100% oxygen exposure.

Abbreviations: HR, heart rate; BP, mean blood pressure; PA, mean pulmonary artery pressure; PCWP, mean pulmonary capillary wedge pressure; RAP, mean right atrial pressure; CPP, coronary perfusion pressure; CO, cardiac output.

— ES_{AREA}/ED_{AREA} . Percent hypokinetic segments represents the number of hypokinetic segments divided by the total number of equiangular segments (64) in one cross-sectional slice. Hypokinesis was defined as a 25% reduction in inward motion of a segment. Data are expressed as mean ± SEM. Statistical analysis was performed with analysis of variance (ANOVA) for repeated measurements and multiple comparison *t*-testing (least significant difference technique). Differences with *P* < 0.05 are considered statistically significant. Power calculations were performed using a standard formula for power for single proportions (5).

Results

During the four study periods, no significant differences were observed in the hemodynamic measurements (Table 1). The arterial partial pressure of oxygen was significantly lower as expected during the periods of ventilation with 70% nitrous oxide or 70% nitrogen. No significant differences were noted in any derived cardiovascular variable (Table 2). Table 3 presents data obtained from analysis of the echocardiographic images. No patient demonstrated a new paradoxical wall motion abnormality during any study phase. Further, no patient developed ischemic change in the surface ECG (II, V₅). No perioperative myocardial infarctions were noted by serial ECGs or creatinine phosphokinase determinations.

One patient did develop global left ventricular hypokinesis on initial exposure to nitrous oxide, which persisted into subsequent study phases. Marked increases in both pulmonary vascular resistance and systemic vascular resistance and an increased end-systolic area were the notable hemodynamic changes associated with nitrous oxide

exposure in this single patient. Systolic dysfunction persisted despite elimination of nitrous oxide and was associated with elevated systemic vascular resistance.

A power analysis of the study was performed assuming a 10% incidence of spontaneous myocardial ischemia during the study period and an 80% probability of nitrous oxide-induced ischemia. The sample size (*n* = 7) yielded a power of 0.95. If nitrous oxide administration and induced ischemia in 50% of the patients in this study, the power decreased to 0.44.

Discussion

Nitrous oxide, employed as an adjunct to both IV and inhalational anesthesia, has been reported to have various effects on cardiovascular performance. Stoeltzing and Gibbs (6) reported decreases in blood pressure and cardiac index and increased systemic vascular resistance after nitrous oxide exposure in patients undergoing heart surgery during morphine anesthesia. After elimination of nitrous oxide, blood pressure increased above prenitrous oxide values, but cardiac index remained depressed and systemic vascular resistance continued to increase. Wong et al. (7), in healthy male volunteers, and Lappas et al. (8), in patients with coronary artery disease, reported similar results in subjects and patients anesthetized with morphine. At cardiac catheterization, Eisele et al. (9) reported that nitrous oxide decreased left ventricular function in patients with poor left ventricular reserve, but no depression was observed in patients with relatively normal function. Balasaraswathi et al. (10), in patients anesthetized with fentanyl, documented that nitrous oxide decreased left ventricular function in patients with poor left ventricular reserve, but not in patients with preserved function. Using a sufentanil-based anesthetic, Michaels and Barash (1) demonstrated that the hemodynamic effects of 70% nitrous oxide in oxygen versus 70% nitrogen in oxygen were similar when administered to patients undergoing aortocoronary bypass grafting. In contrast, Philbin et al. (2), using a canine model of acute coronary constriction, found nitrous oxide to consistently induce regional wall motion abnormalities in the territory supplied by the constricted coronary artery. Despite these abnormalities, no evidence of ventricular dysfunction was detected by routine measurements of hemodynamic performance.

Our study utilizing two-dimensional transesophageal echocardiography revealed no new regional wall motion abnormalities on exposure to 70% nitrous oxide versus 70% nitrogen during the precar-

Table 2. Derived Hemodynamic Performance*

	100% O ₂	70% N ₂ O/O ₂	70% N ₂ /O ₂	100% O ₂
CI (L·min ⁻¹ ·m ⁻²)	2.7 ± 0.2	2.2 ± 0.2	2.5 ± 0.2	2.2 ± 0.2
SVI (ml/beat/m ²)	40 ± 3	35 ± 3	30 ± 3	33 ± 3
SVRI (dynes·sec·cm ⁻⁵ ·m ⁻²)	2422 ± 526	2558 ± 119	2613 ± 171	2796 ± 345
PVRI (dynes·sec·cm ⁻⁵ ·m ⁻²)	212 ± 34	278 ± 40	286 ± 37	247 ± 40
LVSWI (g·m/m ²)	41.8 ± 5.5	32.6 ± 5.4	38.0 ± 5.6	33.7 ± 5.4
RVSWI (g·m/m ²)	5.7 ± 0.7	5.4 ± 1.3	5.9 ± 1.1	4.6 ± 0.9
CaO ₂ (ml O ₂ /100 ml blood)	16.4 ± 0.6	15.2 ± 0.6	14.6 ± 0.5	16.1 ± 0.6

*Mean ± SEM.

Table 3. Echocardiographic Variables*

	100% O ₂	70% N ₂ O/O ₂	70% N ₂ /O ₂	100% O ₂
EF _{AREA} (%)	47 ± 5	45 ± 4	51 ± 7	40 ± 4
% Hypokinetic segments	0.4 ± 0.4	13.6 ± 10.6	7.1 ± 6.6	10.6 ± 9.8

*Mean ± SEM.

diopulmonary bypass period of aortocoronary bypass surgery, although global cardiac function was depressed in one patient. Preoperatively, at cardiac catheterization, cardiomegaly, poor left ventricular function (ejection fraction, 40%), posterior-basal and anterior-apical hypokinesis were noted in this patient. Global hypokinesis was observed after nitrous oxide exposure, which did not resolve on its elimination. In this patient, a progressive increase in systemic vascular resistance was observed during each study phase which was associated with decreasing cardiac index and ejection fraction-area. The increased afterload may have been sufficient to produce global dysfunction in a previously compromised left ventricle. Although we do not believe the systolic dysfunction noted in this patient was a result of myocardial ischemia, we cannot exclude the possibility.

Analysis of hemodynamic data did not reveal significant effects of nitrous oxide on determinants of myocardial oxygen supply and demand. Coronary perfusion pressure did not vary significantly during the four-study phase. This is in distinction to the study of Philbin et al. (2) in which coronary perfusion pressure decreased with nitrous oxide. Although these changes are significant statistically, they are small in magnitude. We do not believe they account for the finding of consistent postsystolic shortening during nitrous oxide exposure.

Echocardiographic signs of myocardial ischemia include decreased systolic wall thickening and regional wall motion abnormalities (11). Regional wall motion analysis is based on the measurement of endocardial excursion. A quantitative approach to

measurement of normal inward motion of the endocardium requires digitization of the end-diastolic (ED) and end-systolic (ES) frames. These are selected by gating the two-dimensional images with a superimposed ECG waveform. The endocardial borders can then be traced on the screen using a mouse or light pen device during diastole and systole. For most analyses, a reference system must then be selected to spatially locate the endocardial borders selected for comparison. The frame of reference allows the endocardial borders to be superimposed on the same video image to calculate endocardial excursion during the cardiac cycle.

Reference systems may be divided into fixed- or floating-axis, depending on whether they attempt to correct for rotational and/or translational movement of the heart during the cardiac cycle. Fixed references may be external to the cardiac image or internal to the myocardial borders. Such fixed coordinates do not attempt to correct for cardiac motion but are used primarily to orient systolic and diastolic endocardial borders to the videoframe. Floating-axis references attempt to correct for cardiac movements within the chest. The center-of-mass (COM) may be calculated for any endocardial outline and may be viewed as a hypothetical center of the endocardium. It is toward this center that every point on the outline moves during systole. If the center-of-mass is calculated for both end-diastole and end-systole, the centers may be superimposed to correct for translational movement.

Schnittger et al. (12) compared 44 different types of reference systems in patients coming to the echocardiography laboratory. These investigators concluded that the floating-axis system was superior for the four-chamber long-axis and short-axis mitral valve views. At the papillary muscle level, the fixed-axis reference system appeared to be superior. Moynihan et al. (13) also compared fixed- versus floating-axis reference systems to quantitate wall motion. The reproducibility for the floating-axis system was superior at the papillary muscle and equal to the fixed-axis

system at the mitral valve level. A second study by these authors revealed that the fixed-axis reference system was superior for localizing regional wall motion abnormalities, but equal to the floating-axis reference system in identifying regional wall motion abnormalities. The preceding studies involved closed chest, nonsurgical subjects.

Durkin et al. (14) studied patients during myocardial revascularization with two-dimensional transesophageal echocardiography to assess wall motion. A floating-axis reference system using center-of-mass corrected for the paradoxical septal motion noted to be universal after cardiopulmonary bypass when a fixed-axis system was employed. These investigators concluded that when significant movement of the heart occurs, such as in the open chest setting, the floating reference system may eliminate artifactual regional wall motion abnormalities. In the absence of significant cardiac translation or rotation, the floating reference may artifactually minimize wall motion opposite a dyskinetic segment. Real questions remain to be answered regarding the optimal reference system in the surgical patient.

The differences between the human and canine studies may be explained as follows. Acutely narrowed coronary arteries of previously healthy dogs may not respond to anesthetics in similar fashion as chronically diseased human coronary vessels. Our patients were also receiving nitrates, β -blocking agents and calcium-entry blockers. A decision to intervene surgically in coronary disease should be preceded by aggressive medical management, and most patients will be taking a combination of these drugs. It is not possible to predict or remove the effects of preoperative drug therapy on an experimental protocol. These drugs could have altered coronary response to nitrous oxide. Although arterial oxygen tension decreased significantly during the periods of ventilation with 30% oxygen, arterial oxygen content remained statistically unchanged, suggesting adequate oxygen delivery. Short axis, cross-sectional views at mid-papillary muscle level selected for this study may have missed ischemic left ventricular regions. We doubt this because the territories supplied by all epicardial coronary arteries are represented in the monitored ventricular cross-section. There is support that this echocardiographic imaging is a sensitive detector of ischemia (15). Lack of ischemia is further confirmed by absence of hemodynamic or electrocardiographic changes as well as lack of contraction disturbances. Cahalan et al. (16), in a study design comparable to our own, were also unable to demonstrate development of regional wall motion abnormalities during nitrous oxide adminis-

tration in subjects anesthetized with fentanyl. Assessment of wall motion in their evaluation was qualitative. Their study took place before operative intervention, whereas our data were obtained during surgical stimulation in the thorax. Nonetheless, the results agree.

In any clinical study with a negative result, the investigator must be concerned with inadequate power when forming conclusions. This study was designed to test the hypothesis that nitrous oxide induces wall motion abnormalities in patients with critical coronary stenosis. Philbin et al. (2), utilizing a canine model of coronary artery disease, demonstrated post-systolic shortening in all dogs subjected to nitrous oxide inhalation. Based on the latter study, we believe that an expected 80% incidence of nitrous oxide and induced wall motion abnormality was reasonable for power analysis. Our study was designed to demonstrate nitrous oxide-induced wall motion abnormalities only if they occurred in most patients, as in the animal model. If nitrous oxide induces myocardial ischemia in a small proportion of patients with coronary disease, this study design lacked sufficient power. Power levels of 0.8 are considered adequate for clinical studies.

In conclusion, under the conditions of our study, addition of nitrous oxide to a high-dose, sufentanil-based anesthetic before cardiopulmonary bypass does not appear to place patients with severe coronary artery disease at risk of developing regional wall motion abnormalities indicative of myocardial ischemia.

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Anesthesia for a Patient with Polymyositis Undergoing Myectomy of the Cricopharyngeal Muscle

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Key Words: COMPLICATIONS—polymyositis.

In 1958, Churchill-Davidson and Richardson (1) found evidence of myasthenic features in two of ten patients with dermatomyositis. Therefore, the authors warned of the use of neuromuscular blocking agents in these patients. Two recent case reports (2,3) show that patients with myositis but without myasthenic features may also respond abnormally to nondepolarizing muscle relaxants. In the first case, the duration of the action of atracurium 0.3 mg/kg, as well as the time from the administration of neostigmine to 98% recovery of the control twitch height, were slightly prolonged in a patient with nonparasitic eosinophilic myositis (2). In the second case, a patient with polymyositis showed prolonged neuromuscular blockade after vecuronium 0.13 mg/kg (3). The authors of the second case report (3) concluded that additional studies of the response of the patients with polymyositis to nondepolarizing neuromuscular blocking agents are necessary to quantitate the magnitude of possible subclinical defects in neuromuscular transmission. The present report describes a normal response of a patient with polymyositis to vecuronium under thiopental-alfentanil-N₂O/O₂ anesthesia for myectomy of the cricopharyngeal muscle.

Case Report

A 67-year-old man with long-standing mild arterial hypertension and a 1.5-year history of polymyositis required myectomy of the cricopharyngeal muscle because of difficulties in swallowing probably due to polymyositis. The diagnosis of polymyositis was based on clinical presentation, elevated serum crea-

tine phosphokinase (CPK) (at maximum 464 IU/L, normal range in men 30-230 IU/L), aldolase concentrations, (at maximum 11.2 IU/L, normal range 1.0-6.5 IU/L), characteristic muscle biopsy, and electromyography. The main clinical symptoms were pain, stiffness, and weakness of the thigh muscles. The biopsy specimen from the left thigh muscle showed lymphocytic infiltration around muscle filaments and thickening of the arterial walls. The electromyographic study showed spontaneous fibrillation in the proximal muscles of the upper and lower extremities. Since establishment of the diagnosis of polymyositis, the patient had been continuously taking corticosteroid medication. At the time of surgery, daily medications included prednisone 5 mg and atenolol 50 mg.

Preoperative physical examination showed the patient to be 182 cm tall, weighing 78 kg, with an arterial pressure of 170/75 mm Hg and heart rate 60 beats/min. Auscultation of the heart and lungs revealed nothing unusual. The ECG was normal. Blood hemoglobin concentration was 14.4 g/dl, and serum levels of electrolytes, creatinine, glutamic oxaloacetic, and glutamic pyruvic transaminases were normal, but concentrations of CPK (398 IU/L) and lactic dehydrogenase (473 IU/L, normal range 200-450 IU/L) were elevated.

Anesthesia

The patient was premedicated with meperidine 80 mg, atropine 0.8 mg, and cortisol 100 mg IM 70 minutes before the start of anesthesia, the duration of which was 110 minutes. Anesthesia was induced with 400 mg thiopental and maintained with five 50-mg bolus doses of thiopental and nitrous oxide and oxygen (3:1). Alfentanil (a total dose of 3 mg) was used for analgesia. Arterial pressure was recorded every 5 minutes with an electronic oscillotonometer (Nippon Colin BP103N Mark III). The heart rate and ECG were continuously monitored. Cardiovascular

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variables remained stable during surgery. Respiration was mechanically controlled with a Servo 900 ventilator, keeping the end-tidal $\text{CO}_2\%$ between 5.5 and 6.0 and the inspiratory $\text{O}_2\%$ between 36 and 38%. Twenty-five minutes before the end of anesthesia, the arterial acid-base status was within normal limits and the Pao_2 was 179 mm Hg.

Neuromuscular Blockade

Intubation was facilitated with a priming dose of 0.8 mg vecuronium followed by a dose of 7.2 mg 3 minutes later. At 2.5 minutes after the second dose, intubating conditions were excellent and intubation was easily accomplished. Neuromuscular blockade was maintained with a 0.02% vecuronium infusion so that the T1% remained between 3 and 15. The total amount of vecuronium given was 16.6 mg, 8.6 mg of which was by infusion. Neuromuscular blockade was continuously monitored and recorded from the right hand (NMT-100, program 87 3267 from Datex-Instrumentarium Oy, Helsinki, Finland). Before administration of vecuronium, 57 mA caused supra-maximal stimulus. The monitor delivered a train-of-four (TOF) stimulus every 20 seconds. After each stimulus, the height of the first twitch as a percentage of its baseline height (T1%), as well as the height of the fourth twitch as a percentage of the simultaneously measured height of the first twitch of the TOF (TR%), were digitally displayed and graphically recorded on a paper. At the end of anesthesia, before reversal of the neuromuscular block with neostigmine 4 mg preceded by glycopyrrolate 0.8 mg, the T1%/TR% was 17/0. One, 2, 3, 4, 5, and 6 minutes after administration of neostigmine and glycopyrrolate, values for the T1%/TR% were 58/12, 73/34, 77/51, 80/61, 80/71, and 83/76, respectively. Four minutes after the end of anesthesia, the patient knew his name and date of birth and was oriented in place and time. The 4-hour recovery room period was uneventful. The patient needed neither analgesics nor other drugs.

Discussion

In a recent study (4), the average amount of vecuronium needed by infusion, after an initial bolus dose to maintain 90% neuromuscular block ranged from 11 to 87 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ (mean 75) during fentanyl- N_2O anesthesia. In the present study the corresponding

figure required to achieve a 85–97% neuromuscular block was 90 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$ under alfentanil- N_2O -anesthesia. Thus, the need for vecuronium of the present patient suffering from polymyositis was in the same range as those reported in patients without polymyositis under comparable anesthesia. Furthermore, Kopman (5) has recently shown that 5 minutes after 0.05 mg/kg of neostigmine the T1% recovered from 9.6 to 83 and the TR% was 60 at 5 minutes in normal patients. Thus the present increase in T1%/TR% from 17/0 to 80/71 5 minutes after 0.05 mg/kg of neostigmine indicates that the recovery from the vecuronium-induced neuromuscular block was not prolonged in our patient with polymyositis. The present result was expected, because the pathologic changes of polymyositis most probably occur distal to the neuromuscular junction and the disease affects neither the function nor the degradation of acetylcholine. The present case report clearly shows that at least some patients with polymyositis tolerate vecuronium well.

As far as we know there are no earlier reports concerning the responses of patients suffering from polymyositis with elevated CPK to agents capable of triggering the onset of malignant hyperthermia (MH). Because of the elevated CPK in the present case, we avoided such triggering agents of MH as succinylcholine and halogenated hydrocarbons. The decision was supported by Farag and others (2) who avoided all triggering agents of MH in a patient suffering from eosinophilic myositis with a high resting level of serum CPK.

Our purpose in presenting this report was to contribute to the knowledge of the responses of the patients with polymyositis to nondepolarizing neuromuscular blocking agents.

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Improvement in Blood Flow During Lower Extremity Microsurgical Free Tissue Transfer Associated with Epidural Anesthesia

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Key Words: ANESTHETIC TECHNIQUES—epidural. ANESTHESIA—peripheral vascular. SURGERY—peripheral vascular.

Patients undergoing reconstructive surgery involving free tissue transfer from one part of the body to another provide an interesting challenge to the anesthesiologist. The immediate success of this procedure depends on maintenance of adequate perfusion through the microsurgical arterial and venous anastomoses. A technique that optimizes blood flow to the free flap and minimizes the possibility of vascular spasm and flap ischemia is needed. A case is presented in which a patient developed intraoperative flap ischemia. The problem was quickly and reproducibly eliminated by reinjection of an epidural block, thereby possibly preventing loss of the free muscle flap.

Case Report

A 53-year-old, 100-kg man with chronic draining osteomyelitis of the right tibia was brought to the operating room for a rectus abdominis free muscle flap transfer to the distal third of the right leg. Preoperative angiography showed patency of only the posterior tibial artery with good distal run-off. Physical evaluation showed a physical status II patient with all laboratory values within normal limits. The patient preferred regional anesthesia, and epidural anesthesia was planned.

The patient was premedicated with morphine sulfate 10 mg and scopolamine 0.4 mg IM. On arrival in the operating room his arterial blood pressure was

110/65 mm Hg. An epidural catheter was placed at the L3-L4 interspace. A test dose of 3 ml bupivacaine 0.5% with 1:200,000 epinephrine was injected. After this negative test dose, 20 ml bupivacaine 0.75% was administered until an anesthetic level of T4 was obtained. Fifteen minutes after surgical incision was made, the patient complained of discomfort above the level of the epidural block. This was caused by surgical traction applied while harvesting the rectus abdominis free muscle flap, and there was no acute incisional pain. The block was retested at this time, and was again found to extend to T4. The patient had no sensation or motor function in the lower extremities. Because of the patient's discomfort and anxiety, general anesthesia was induced with thiopental 250 mg followed by succinylcholine 140 mg and tracheal intubation. Anesthesia was maintained with nitrous oxide and oxygen, fentanyl, lorazepam, and atracurium. No volatile anesthetics were used. The patient remained hemodynamically stable with blood pressure 110/60 mm Hg and heart rate 70 beats/min for the next 3 hours.

After that time period, the patient's blood pressure increased to 130/70 mm Hg, and heart rate increased to 100 beats/min. Simultaneously with this hemodynamic change, the surgeon noted absence of arterial pulsation in the artery supplying the transferred muscle flap distal to its anastomosis to the posterior tibial artery. This was confirmed by loss of signal from a 20 MHz ultrasonic Doppler probe used to monitor blood flow into the free muscle flap. However, inspection of the arterial and venous microvascular anastomoses under the operating microscope revealed both to be patent without thrombosis. At this time, 5 ml bupivacaine 0.75% was injected into the epidural catheter. No other change was made in the depth of anesthesia. Within minutes, arterial pulsation in the inflow artery to the free muscle flap resumed, and the Doppler flow probe signal returned. Blood pressure and pulse rate returned to normal. Forty-five minutes later, blood pressure increased suddenly to 190/110 mm Hg, heart rate in-

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creased to 120 beats/min, and the 20 MHz Doppler flow probe signal again indicated diminishing flow and then no flow. Five milliliters bupivacaine 0.75% was again injected into the epidural space. Again, no other change was made in the depth of anesthesia. With this injection, blood pressure and heart rate returned to normal, and adequate blood flow to the muscle flap was quickly reestablished with restoration of a normal Doppler signal.

On completion of the operation the patient awakened and was extubated uneventfully. He was brought to the postanesthetic recovery room, where vital signs and the Doppler probe recording of arterial inflow to the free muscle flap remained normal. Continued intermittent injection of 5 ml bupivacaine 0.125% epidurally for analgesia was associated with maintenance of good blood flow in the operative site throughout his overnight recovery room stay. Epidural analgesia was continued for 24 hours after completion of the operation and then was terminated when blood flow appeared to be adequate without reinjection of the epidural catheter. The patient maintained adequate blood flow to the graft and was later discharged from the hospital with a successful free tissue transfer.

Discussion

Previous recommendations for anesthetic management of patients undergoing microsurgical free tissue transfer include maintenance of normothermia, normovolemia, normal hemoglobin concentration, and analgesia (1). In addition to these nonspecific supportive measures, epidural anesthesia has been advocated in operations involving free tissue transfer to a lower extremity because of the effects of epidural blockade on the sympathetic response and skin blood flow (1). However, there has been no clinical evidence to date to support the hypothesis that epidural anesthesia improves blood flow in free tissue transfers to the lower extremity. That epidural anesthesia might be of use is suggested by the report that lumbar sympathectomy improved the outcome of reconstructive vascular surgery in the lower limb in 34 patients (40 limbs) undergoing aorto-iliac surgery or femoropopliteal reconstruction (2). Blood flow was measured with electromagnetic flow probes located on vessels in areas of reconstruction. All patients received surgical lumbar sympathectomies after completion of arterial reconstruction. In 27 limbs there was evidence of vasoconstriction before sympathectomy, with significant increases in blood flow after sympathectomy. Even in the presence of extensive

vascular disease, sympathectomy usually increased peripheral blood flow. In only five limbs did sympathectomy fail to improve low flow states, all because of fixed outflow resistance (e.g., atheromatous plaques). In another study, epidural anesthesia after reconstructive vascular surgery significantly increased graft blood flow (3). This finding indicates that epidural blockade, a reversible and relatively safe technique, improves blood flow in a manner comparable to surgical sympathectomy.

It is tempting to assume that the findings in the present patient were principally or even entirely due to the sympathetic blockade induced by the epidural anesthesia. However, there is a complex relation between pain, the sympathetic nervous system, and peripheral and muscle blood flow. In this patient, we cannot know with certainty whether the beneficial effect on blood flow to the free muscle flap was due purely to sympathectomy. The sensory component of the epidural block may be important as well. Past studies have looked at this relation in the context of nerve blocks for relief of chronic rest pain in patients with vascular insufficiency (4). The effects of acute, incisional pain on blood flow through free muscle and skin flaps, as well as the relative effects of sympathetic and sensory blockade on flap blood flow, have not yet been investigated. Another possible explanation for the observed effect of the epidural injection is an interaction of the epidural block with another component of the anesthetic, such as nitrous oxide. Nitrous oxide activates the sympathetic nervous system (5,6). However, the concentration of nitrous oxide was constant throughout the case. Whether the improvement in blood flow noted with epidural injection is dependent on the presence of nitrous oxide requires further study. In addition, although the absorption of bupivacaine from the epidural space into the blood with concomitant effects on peripheral blood flow and/or microvascular function may be involved, the rapid time course of blood flow improvement after reinjection of the epidural block tends to negate this.

Free tissue transfer operations are becoming increasingly frequent with the development of sophisticated microsurgical techniques. Because surgical success is critically dependent on blood flow through the arterial and venous micro-anastomoses, prevention of vasoconstriction in the limb vessels is of great importance. For this reason, continuous epidural blockade in patients undergoing this type of surgery may offer an important improvement in intraoperative and postoperative management. Additional study is needed to confirm this belief as well as to

further elucidate the physiology of blood flow in denervated free skin flaps and muscle flaps.

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Heart-Synchronized Ventilation during General Anesthesia for Extracorporeal Shock Wave Lithotripsy

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Key Words: ANESTHESIA, UROLOGIC—lithotripsy. VENTILATION, HEART—synchronized.

Extracorporeal shock wave lithotripsy (ESWL) has gained worldwide acceptance during recent years as a noninvasive technique for the destruction of renal calculi. Because the procedure is painful, anesthesia is necessary. General anesthesia, as well as spinal or epidural anesthesia (1,2) and, even intercostal block with local infiltration (3) have been used with success.

During spontaneous breathing or conventional mechanical ventilation, stone movement with respiratory motion may create a problem, especially if the stone is fairly small. With significant stone movements the shock waves must be fired with less precise focus, with more energy released in surrounding tissue with potential damage (edema), prolongation of the procedure, and possibly incomplete destruction of the stone. High-frequency ventilation has been used as one means to reduce stone movements (4-6). In some patients significant aortic pulsation may, however, also contribute to stone movements, especially stones on the left side. If heartbeats are used to trigger not only the shock waves but also the ventilator, even these movements may be counteracted. We describe our results using the technique of heart-synchronized ventilation, with which the ECG signal from the patient triggers both inspiration on the ventilator and the firing of shock waves.

Materials and Methods

Twenty-two patients (ASA I-II), 12 men and 10 women (11-70 years old), with nephrolithiasis of the upper urinary tract were studied. Eight patients were

smokers. Our standard technique for ESWL is epidural analgesia, but these 22 patients were given general anesthesia due to previous back problems, young age (11 years), or refusal to accept epidural analgesia. Verbal consent was obtained from all patients, and the study was approved by the Ethics Committee.

Anesthesia

Promethazine 25 mg and meperidine 25-50 mg were given IM as premedication approximately 1 hour before anesthesia. In one case, an 11-year-old boy, diazepam was given rectally. ECG electrodes were attached to the skin on the shoulders and on the left side of the thorax under watertight adhesive draping. An IV catheter was inserted, and patients were then given 0.1 mg fentanyl followed by 1 mg pancuronium. After preoxygenation, thiopental 4-7 mg/kg was given until the eyelash reflex was abolished, after which succinylcholine 1 mg/kg was given. Tracheal intubation was performed with cuffed endotracheal tubes, inside diameter (ID), 7.5 mm (for the 11-year-old boy, 7.0 mm), 23 cm in length. Before the patients were placed in the hydraulic support frame, additional doses of pancuronium (up to 0.07 mg/kg) and fentanyl (0.05-0.1 mg) were injected. During the treatment in the tub, an additional dose of fentanyl 0.05-0.1 mg was given.

Ventilation was maintained with a Servo ventilator 900 C (Siemens-Elema, Solna, Sweden) using 35% oxygen and 65% nitrous oxide. Minute ventilation was set at 4.5 L/m² with an initial frequency of 12 breaths/min. Each limb of the ventilator tubing (Hytrel, Siemens-Elema) was 150 cm in length, ID 22 mm. No humidifier was incorporated into the system. The transducer of an infrared carbon dioxide analyzer (CO₂-Analyzer 930, Siemens Elema) was incorporated between the Y-piece and the proximal end of the endotracheal tube adaptor. The deadspace of the endotracheal tube and its adaptor, the CO₂ analyzer

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Table 1. Ventilatory Characteristics of the Heart-Synchronized Ventilation Unit*

Breaths per minute	Programmed minute volume (L/min)	Volume delivered (L/min)	Difference (%)
52	10	10	0
60	10	11.4	+14
70	10	13.3	+33
80	10	15.2	+52
90	10	17.1	+71
100	10	19.0	+90
105	10	19.9	+99

*Set inspiratory time on the Servoventilator 25%. A breathing rate <52 breaths/min implies that delivered volume will be less than programmed volume.

cuvette, and Y-piece was measured to 38 ml. End-tidal CO₂ (PETCO₂) values were corrected for the presence of nitrous oxide (7). The tubing was checked for leaks. Signals from the CO₂ analyzer, gas flowmeter, and airway pressuremeter (incorporated in the ventilator) were fed into a high-frequency response ink-jet recorder (Mingograph 82, Siemens-Eléma).

A heart-synchronized ventilatory unit (prototype, dimensions 15 × 8 × 5 cm, Siemens-Eléma) was connected to the electronic unit of both the ventilator and the ECG monitor (Sirecust 404, Siemens-Eléma). An R-wave triggered input signal is fed to the heart-synchronized ventilatory unit and processed. By simply turning an on-off switch on the device to the on position, an R-wave synchronous output signal can be fed to the Servoventilator to initiate inspiration. After 0.285 second (irrespective of ventilatory frequency), another signal from the device inhibits the inspiration. The device thus enables ventilation to be synchronous with heart activity with a ventilatory frequency equal to the heart rate or to be set on the ventilator in the usual way. If the heart rate increases above 105 beats/min, one breath is given for every other heartbeat. When heart-synchronized ventilation is used, the device automatically compensates for an increase in the deadspace ventilation independently of the dialed minute volume according to the data provided by the manufacturers (shown in Table 1). (Further data are given under Results and in Fig. 1.)

Procedure

When the patient had been mechanically ventilated for 15 minutes at a rate of 12 breaths/min, an arterial blood sample (radial artery) was obtained and blood gas analysis (control value) immediately carried out (Radiometer ABL II, Copenhagen, Denmark) with correction for body temperature as measured with a

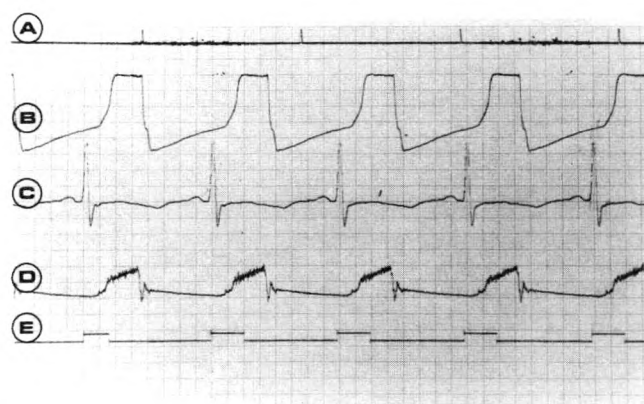


Figure 1. Original continuous tracings obtained from the CO₂ analyzer from one patient. A, time scale. The distance between two spikes corresponds to 1 second. B, airway flow, C, ECG m; D, airway pressure, E, steering signal to the lithotripter.

nasopharyngeal probe. The patient was then transferred to the hydraulic chair and immersed in the water tub. In 16 of the 22 patients (5 with previous surgery of affected kidney, 11 without previous surgery), measurement of stone movements during conventional ventilation was performed. With fluoroscopy the position of the stone could be identified and the largest movement in the craniocaudal direction under undisturbed ventilation noted. Heart-synchronized ventilation was then started, and a similar measurement of stone movement was made. In 6 of the 22 patients, these stone movements were not measured. Further arterial blood gas analysis was made 15, 30, and 45 min after commencement of heart-synchronized ventilation. At the end of the procedure, N₂O was discontinued and muscle paralysis reversed with neostigmine 2.5 mg and atropine 1 mg. After tracheal extubation the patient was transferred to the recovery room.

Statistics

Student's paired *t*-test was used to determine the statistical significance of differences in stone movements with conventional ventilation and heart-synchronized ventilation.

Results

In Figure 1 the relation between ventilation and heart activity during heart-synchronized ventilation is demonstrated. This original tracing from one of the patients shows the ECG signal and its relation to flow and pressure in the ventilator and to the steering

Table 2. Stone Movements (in mm) during Conventional Ventilation (12 breaths/min) and during Heart-Synchronized Ventilation in Nonoperated Patients (11/22 patients) and in Patients Who Had Previously Undergone Renal Surgery (5/11 patients) on the Same Side*

	Conventional ventilation	Heart-synchronized ventilation
Nonoperated (<i>n</i> = 11)	18.5† (13–24)	2.8 (2–5)
Operated (<i>n</i> = 5)	13.8 (9–17)	3.1 (2–4)

*Six patients were not tested.

†Mean and range in parentheses.

signal to the lithotripter unit. The heart-synchronized ventilatory unit was set to start inspiration about 0.08 second after the peak in the R-wave and at the end of expiration. This coincides with the early part of the steering signal to the lithotripter unit initiating the shock wave with a delay of 0.02 second. The signal for the actual generation of the shock wave could not be obtained. Mean duration of heart-synchronized ventilation was 38 minutes (range 21–75).

In Table 2 the results from those 16 of 22 patients in whom stone movements were measured are presented. The results show that a highly significant reduction ($P < 0.001$) in stone movements occurred with heart-synchronized ventilation compared to conventional ventilation. This was found both in patients with previous surgery on the actual kidney and in patients without previous surgery.

Results of arterial blood gas analyses are shown in Table 3. After an initial reduction in mean PaO_2 and an increase in mean PaCO_2 registered after the commencement of heart-synchronized ventilation, stabilization occurred in blood gas tensions. The highest PaCO_2 recorded, 6.8 kPa (51.1 mm Hg), was in a 60-kg male smoker with a heart rate of 76 beats/min (= ventilatory frequency). The baseline PaCO_2 value was 5.3 kPa (39.8 mm Hg). The lowest PaO_2 recorded (8.5 kPa = 63.9 mm Hg) was in a 90-kg male smoker, ventilated with a frequency of 73 breaths/min. His baseline PaO_2 was 14.5 kPa (109.0 mm Hg). Four patients were ventilated at a rate below 60 breaths/min (55–59); the PaCO_2 values in these patients ranged from 4.3 to 5.9 kPa (32.3–44.4 mm Hg). Maximum heart rate (= ventilatory frequency) was 82.

Discussion

This study shows that heart-synchronized ventilation may be a useful alternative mode of ventilation dur-

ing ESWL. Stone movements in the cranial-caudad direction were reduced with this ventilatory technique as when using high-frequency ventilation (4,5). In our measurements, stones moved five to six times less than during conventional ventilation. Contrary to experience during high-frequency ventilation, however, all shock waves hit the stone in the same phase of ventilation with heart-synchronized ventilation and, presumably, if ventilatory compliance does not change, at the same place. Focusing the shock waves, especially when treating relatively small stones, should therefore be made easier and, theoretically, a higher proportion of the shock waves should hit the target. This in turn should reduce the number of shock waves required, rendering treatment less traumatic and less expensive (5). The restricted nature of this study, however, allows no such conclusions to be made.

Monitoring of ventilation is necessary when using heart-synchronized ventilation. As shown in Table 3, there was a large interindividual variation even though patients were ventilated in a standardized fashion. With higher ventilatory frequencies, dead-space increased. This was compensated for in this study, however (see Table 1), and in only one patient were abnormally high PaCO_2 values seen (6.7, 6.8, and 6.6 kPa, respectively; 50.4, 51.1, and 49.6 mm Hg). Not even in patients with heart rates below 60 beats/min (four patients) did we observe excessive changes in blood gas tensions. Oxygenation must, however, be monitored during this technique by, for example, pulse oximetry. In the present study there was a discrepancy between PETCO_2 and arterial PCO_2 , especially at higher frequencies (Table 3). This has been shown before (8,9). One possible solution to this problem in the clinical setting would be to briefly interrupt heart-synchronized ventilation in favor of the normal original IPPB setting thus enabling more representative PETCO_2 values (9,10).

In this study special attention was paid to patients with a history of smoking; they had the lowest PaO_2 values and highest PaCO_2 values. It is known that in smokers the PaCO_2 - PETCO_2 gradient increases with age (11), and we believe that smokers should be given a higher FIO_2 and larger minute volumes when using heart-synchronized ventilation.

In conclusion, provided adequate respiratory monitoring can be accomplished, general anesthesia using heart-synchronized ventilation may be an important alternative to other techniques for managing ventilation during ESWL and should be especially valuable when treating difficult stones and where undue stone movement may lead to the risk of damaging the lung, e.g., in children (12). Furthermore, this ventilatory

Table 3. Arterial Blood Gas Tensions, End-Tidal CO₂ Tension (P_{ET}CO₂), and Ventilatory Frequency during Conventional Ventilation and at Various Time Intervals after the Start of Heart-Synchronized Ventilation.

	Control values (n = 22)	Time after the start of heart-synchronized ventilation (min)		
		15 (n = 22)	30 (n = 20)	45 (n = 12)
Pao ₂ kPa	18.5 (10.9–31.1)*	15.3 (9.0–27.7)	15.2 (8.8–26.5)	13.8 (8.5–28.1)
mm Hg	139 (81.9–233.8)	115.0 (67.7–208.3)	114.3 (66.2–199.2)	103.8 (63.9–211.3)
Paco ₂ kPa	4.3 (3.5–5.4)	5.1 (3.7–6.7)	5.2 (3.7–6.8)	5.1 (3.5–6.6)
mm Hg	32.3 (26.3–40.6)	38.3 (27.8–50.4)	39.1 (27.8–51.1)	38.3 (26.3–49.6)
P _{ET} CO ₂ kPa	3.7 (3.1–4.4)	3.7 (3.0–4.6)	3.8 (2.9–5.0)	3.8 (3.0–4.4)
mm Hg	27.8 (23.3–33.1)	27.8 (22.6–34.6)	28.6 (21.8–37.6)	28.6 (22.6–33.1)
Ventilatory frequency (breaths/min)	12	68 (56–82)	70 (59–79)	69 (56–80)

*Mean and range in parentheses.

technique may, when fully developed, be of great importance when shock wave therapy is used for gallbladder stones (13,14), where synchronous diaphragmatic descent may bring basal parts of the lung into the field of the shock waves.

We would like to thank Bo Dahlström, Siemens-Elema, Solna, Sweden, for constructing the heart-synchronized ventilation device.

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Letters to the Editor

Humidifier Malfunction—A Cause of Anesthesia Circuit Occlusion

To the Editor:

We wish to report two untoward incidents occurring with the use of the Advanced Vapor-Phase Humidifier Heater (Fig. 1).

Case Report #1. A 20-year-old mentally retarded male was scheduled for split thickness skin grafts to both feet. The humidifier was incorporated into an adult anesthesia circle system with the tubing from the inspiratory port of the anesthesia machine connected to the upper port of the transfer chamber of the humidifier, and with the tubing from the side (outlet) port of the humidifier thus becoming the inspiratory limb of the circle system. Preparation and checking of anesthesia equipment, including the circuit, had been carried out. A delay in transport of the patient resulted in the humidifier being left on for approximately 30–45 minutes before use of the circuit. After intravenous induction of anesthesia, attempts to ventilate the patient proved impossible. The patient was promptly intubated, but further attempts to ventilate the patient through the endotracheal tube proved also to be impossible. At this time, high airway pressures of approximately 50–60 cm H₂O were noted on the pressure gauge located on the absorber head, the compliance of the reservoir bag comparatively decreased with the inspiratory limb from the outlet port of the humidifier to the patient blocked, and very little chest wall movements if any, were seen; neither were any breath sounds heard. An immediate further check of the circuit system showed the plastic tube exiting from the humidifier to the patient (inspiratory limb) had melted, causing the lumen to be occluded (Fig. 2). Disconnection of the humidifier from the system and use of a new anesthesia circuit allowed normal ventilation of the patient.

Case Report #2. Several weeks later another of the same type of Advanced Vapor-Phase Humidifier Heaters malfunctioned and caused occlusion of another circuit. This time the humidifier unit was left on for approximately 10 minutes at the completion of a procedure and, when the machine and a new circuit were being prepared and checked for the following case, the used circuit was noted to have melted and caused the same type of occlusion as in Case Report #1.

Despite the Operators Manual claim that the humidifier



Figure 1. Advanced Vapor-Phase Humidifier Heater.

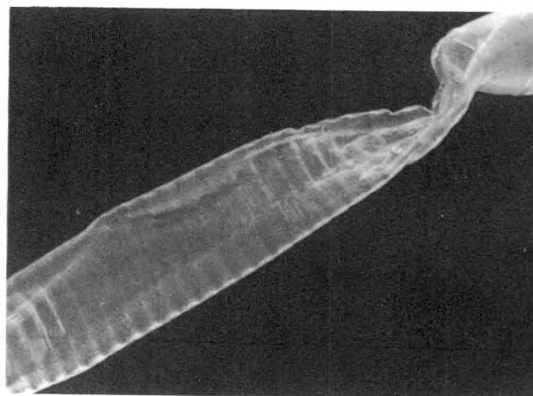


Figure 2. Occluded lumen of plastic tubing coming from the outlet (side) port of the humidifier in case #1.

is equipped with a secondary electrical shut-off switch, and a thermofuse incorporated in the design to disconnect the humidifier in case of internal malfunction or overheating, neither one or perhaps both of these safety devices functioned in our units.

Like others before us who have encountered mishaps due to lack of or incomplete equipment and circuit checking immediately before induction of anesthesia, we cannot emphasize strongly enough the importance of this, along with continued vigilance, at all times.

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In Response:

A review of the photographs indicates a tubing collapse, which is the typical result of operating many heated humidifiers with little or no gas flow. In this situation, the heated water vapor is not transported through the circuit but instead is concentrated in the transfer chamber and adjacent tubing. The vapor temperature rises to the softening temperature of the tubing, causing distortion and potential occlusion.

The heaters did not malfunction. The electrical safety systems monitor the heater platen temperatures. These temperatures remain constant whether there is gas flowing or not. Heated humidifiers are designed to be operated when gas is flowing. Gas flow should be initiated before turning on the heater and the heater should be turned off before interrupting the flow of gas. For Vapor-Phase heaters, there is no need for an extended warm-up period.

We agree with the authors (1) that circuit integrity must be continually monitored during operation of heated humidifiers. This is especially important whenever the gas flow has intentionally or inadvertently been interrupted.

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Vaporizer Fill System Leak

To the Editor:

On three separate occasions, we have observed premature emptying of model 19.1 anesthetic agent vaporizers (North American Dräger, Telford, PA) equipped with a pin-indexed fill system.

On one such occasion, examination of the empty vaporizer revealed that the filler-port plug chain had restricted the movement of the fill valve, preventing its closure. Although the filler-port plug was tightly in place, iso-flurane-laden gas was able to leak out of the vaporizer into ambient air.

Because other anesthetic vaporizers do not require a filler-port plug and it appears that this plug serves no other independent function, the user might assume that the plug on the Dräger assembly is a safety backup to the fill valve. However, leakage of anesthetic agent may occur if either the fill valve or the filler-port plug are unsecured. Although the

operator's manual instructs the user to close the fill valve and to fully insert and tighten the filler-port plug in place after filling, clinicians need to be aware of the consequences of not following this procedure.

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Pulse Oximetry to Determine Oxygenation in a Patient with Pseudohypoxemia

To the Editor:

Pseudohypoxemia is a condition that is not widely appreciated. It occurs in patients with leukemia or thrombocytosis and results in measured arterial blood gas tensions that do not reflect the true level of oxygenation. We found pulse oximetry to be useful in diagnosing this entity.

A 72-year-old man with stage IV chronic lymphocytic leukemia presented with mild dyspnea and splenomegaly. His hematocrit was 22%, white blood cell count was 713,000 cells per ml (97% lymphocytes) and the platelet count was 80,000. Arterial blood gas tensions while breathing room air included a pH of 7.43, P_{aO_2} 48 mm Hg, P_{CO_2} 40 mm Hg, and an oxygen saturation of 84%. Pulse oximetry revealed a saturation of 93%. A subsequent, room air, arterial blood gas sample immediately placed in ice and quickly processed revealed a P_{aO_2} of 67 mm Hg and a saturation of 92%. The diagnosis of pseudohypoxemia was made. The patient subsequently underwent an uneventful splenectomy.

The accuracy of a P_{aO_2} measurement in a blood sample is influenced by the temperature of the sample, the initial P_{aO_2} , the white blood cell count, and the interval from drawing the sample to processing it (1,2). Pseudohypoxemia is a phenomenon that has been described in patients with leukemia and thrombocytosis (3). In leukemic patients, the rate of decrease of P_{aO_2} was more rapid in samples maintained for 60 minutes at 22°C than in those maintained at 20°C, whereas in the non-leukemic control group there was no significant decline in oxygenation at either temperature. White blood cells and platelets account for most of the oxygen utilized in a blood sample. The type and maturity of the leukocyte is an important factor for increasing oxygen utilization. The monocyte has the greatest appetite for O_2 , followed by the granulocyte and lymphocyte. As the cells become more mature, the consumption of oxygen increases for the monocyte and declines for the granulocyte and lymphocyte. Adding sodium fluoride to the heparinized blood will prevent glucose and oxygen uptake by the leukocytes (4). Sodium fluoride is contained in the orange-topped blood sample tube used for serum glucose.

Pseudohypoxemia, though previously described, is not frequently recognized. When evaluating blood gas tensions from patients with leukemia or thrombocytosis, this condition must be kept in mind. Samples from this group of patients should be iced or, preferably, mixed with a small amount of sodium fluoride. The pulse oximeter is an invaluable diagnostic aid in this situation.

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Ischemic Digital Skin Necrosis: A Complication of the Reusable Nelcor Pulse Oximeter Probe

To the Editor:

Pulse oximeters have become very popular monitors. This is due in part to their low risk to the patient. The only reported complications from pulse oximeter probes involved three infants and consisted of a localized skin burn, an area of mild skin erosion, and an area of hyperpigmentation (1). We wish to describe a case of ischemic skin necrosis in a critically ill patient after use of a nondisposable pulse oximeter probe (DS-100A, Nelcor, Inc., Hayward, CA).

The patient was a 74-year-old woman who had undergone a lung lobectomy on hospital day 3. After tracheal extubation, she returned to the intensive care unit (ICU) with a left radial arterial catheter in place. On hospital day 7 she required reintubation of the trachea and mechanical ventilation for respiratory insufficiency. Continuous monitoring of arterial oxygen saturation was initiated at this time using a Nelcor N-100 pulse oximeter with a non-disposable "clip-on" finger probe, and the probe was periodically moved from one finger to another. A right radial arterial catheter was placed, the left one having been removed on day 5. Her course was complicated by right leg ischemia requiring fasciotomy and femoral to femoral arterial cross-over bypass graft on day 9. On day 12 she developed septic shock and required epinephrine and dopamine infusions for 48 hours. Blood pressure during this time ranged from 80/40 to 120/60 mm Hg. Neuromuscular paralysis was

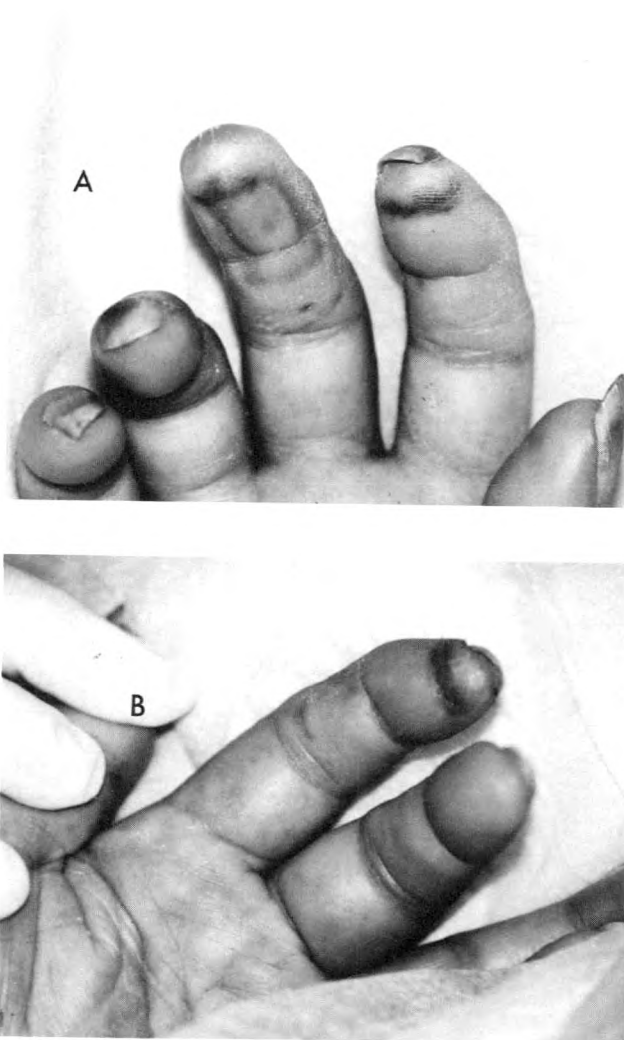


Figure 1. Lesions of the right distal index and middle fingers (A), and the left index finger (B), resulting from pressure exerted by a "clip-on" pulse oximeter probe. Note that the outline of the probe remains impressed into the right middle finger.

required for three days to facilitate mechanical ventilation. On day 17 the right radial arterial catheter was removed and a left radial artery catheter was placed.

On day 19 ischemic changes involving the right index and middle fingers and the left index finger were noted. The lesions on the three fingertips were initially thought to represent embolic infarcts; however, on removal of the pulse oximeter probe to evaluate the right middle finger, the imprint of the probe and the area of necrosis were found to coincide (Fig. 1A). A similar pattern of skin infarction was seen on two other fingers where the probe had previously been placed. At this time the nondisposable probe was replaced with a disposable "tape-on" probe. No data were available on the length of time the nondisposable "clip-on" probe remained in place on any given digit.

The lesions on all involved fingers consisted of a linear area of ecchymotic skin approximately 2 mm × 10 mm on the ventral surface of the finger with a corresponding small ecchymotic area just proximal to the nail bed on the dorsum

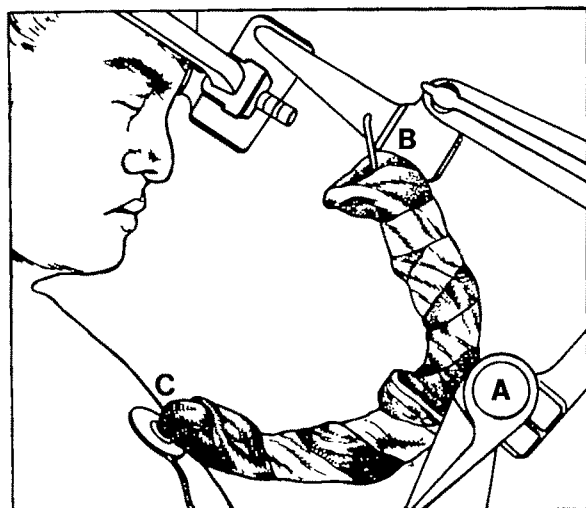


Figure 1. An endotracheal tube stylet is wrapped in a surgical towel, which is then circumferentially wrapped with tape. The placement of the towel-wrapped stylet between points A and B on the head holder applies sufficient pressure on the Doppler sensor (position C) to assure contact between precordium and sensor adequate for proper function of the sensor.

of the finger. The lesions of the right index and left middle fingers had completely resolved within 5 days of discovery; however, the necrotic area on the ventral surface of the left index finger (Fig. 1B) had not healed at the time of the patient's death from multiple organ system failure on day 33.

Pressure, shearing forces, moisture, and friction have been implicated in the pathogenesis of pressure ulcers (2). In normotensive subjects the skin is able to autoregulate blood flow in the presence of 10–30 mm Hg of externally applied pressure; however, autoregulation over this pressure range results in skin blood flow values of only 31–35% of normal. Thereafter, with increasing externally applied pressure, blood flow declines rapidly, resulting in blood flow values of <9% of normal once applied pressure exceeds 60 mm Hg (3). Either high pressures for short periods or lower pressures for longer periods may cause tissue ischemia (4). The most important means of preventing tissue damage, when pressure is unavoidable, is by intermittent relief of the pressure (2).

The risk of tissue ischemia from pulse oximeter probes may be increased when the probe is in place for days, as often occurs in ICUs. Other factors that might increase risk include compromised perfusion of the extremities secondary to low flow states, intra-arterial catheters, or intravenous infusions of vasoconstrictors. We think that the lesions seen in our patient represent areas of skin infarction secondary to pressure from the pulse oximeter probe, and were not the result of skin maceration. The pulse oximeter probe functioned reliably. Moreover, it had not been modified or taped in any way to increase pressure applied to the finger to prevent its displacement.

We suggest that the Nelcor nondisposable probe should be used with caution in ICU patients with significant peripheral vascular disease, and in patients requiring infusions of

vasoconstrictors. Instead, use of a "tape-on" probe, or one of its reusable modifications (5,6) should be considered.

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Reliable Precordial Doppler Monitoring in the Seated Position

To the Editor:

The importance of precordial Doppler monitoring during surgical, especially intracranial procedures in the seated position, is without question. A common problem encountered is the inability to maintain contact between skin and Doppler probe that is adequate for the production of audible heart sounds. Gravity alone often results in displacement of the probe from the precordium when simply taped to the chest wall. We have found an easy and reliable solution to this problem. A pliable endotracheal tube stylet is wrapped in a surgical towel that is then circumferentially wrapped with tape. The stylet is then interposed between points A and B on the head holder apparatus and the probe (point C; Fig. 1). Manipulation of the semi-rigid stylet between these points A, B, and C permits maintenance of enough pressure at C to assure continual presence of audible heart sounds. The stylet offers the apparatus support and pliability. The towel wrapping lends sufficient traction to hold the stylet in place and makes direct contact to the Doppler probe. A strip of adhesive tape over the probe may be used to secure the probe's position on the chest but is not relied on for adequate contact between precordium and sensor. The method has proven effective and reliable for maintenance of proper functioning of the precordial Doppler during neurosurgical procedures in the seated position.

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Appropriate Techniques for Airway Management of Emergency Patients with Suspected Spinal Cord Injury

To the Editor:

While we would like to respectfully express skepticism about the proposal recently made by Gorback (1) regarding manipulations of the endotracheal tube (ETT) cuff to achieve blind nasal intubation, we would, more importantly, like to protest the fact that he, along with so many other anesthesiologists, continues to automatically assume that nasotracheal intubation is either necessary or desirable in patients with suspected or actual spinal cord injuries. As clinicians at the Shock Trauma Center of the Maryland Institute for Emergency Medical Services Systems (MIEMSS), we appreciate the difficulty of intubating the trauma patient with suspected cervical spine instability. Each year since 1983, more than 600 patients with suspected or actual spinal cord injury (SCI) requiring emergency intubation have been admitted to our facility, the statewide referral center for neurotrauma. Predominately using an oral intubation technique as an alternative to nasal intubation, we have afforded safe and efficient airway management to this large patient population.

Difficulties encountered when using blind nasal intubation techniques have prompted the development of various modifications using the tactile, visual, and auditory senses. Additionally, combinations of techniques can be used to improve the efficacy of blind nasal intubation if one feels compelled to use this approach. Although some anesthesiologists consider nasal intubation to be the ideal approach for securing the airway in a patient with cervical SCI, we believe this technique may be contraindicated in the majority of traumatically injured patients. Nasal intubation (blind or fiberoptically guided) is associated with complications and limitations. Nasal intubation should not be used if the patient is apneic, nor should it be used if the patient has a basilar skull fracture because bacteria and foreign materials (including the ETT) could enter the cerebral subarachnoid space through the skull defect. Nasal intubation may induce nosebleeds, which may be aggravated by dilutional coagulopathy. Nasally intubated patients are at risk for postoperative sepsis due to sinusitis. Nasal intubation should not be performed in frightened, inebriated, obtunded, and combative patients, who may thrash about during intubation and cause further damage to a cervical SCI.

Concerning Gorback's technique of blind nasal intubation, we have several comments:

1. The true reliability of this technique is questionable. Gorback cites *one* case report and states that studies of lateral centering of the ETT in the hypopharynx were *not* conducted on cadavers.
2. This technique would seem to stimulate airway reflexes and cause the patient to move when the ETT cuff in the hypopharynx is inflated. Stimulation of airway reflexes by an ETT in the pharynx may induce retching and



Figure 1. Technique of oral endotracheal intubation using Manual In-Line Axial Traction (MIAT). Patient is immobilized on long spine board with anterior portion of semi-rigid (Philadelphia) collar removed. Cricoid pressure is applied, as one trauma team member provides MIAT, the anesthesiologist prepares to perform standard laryngoscopy and oral intubation. (From Stene JK. Anesthesia for the critically ill trauma patient. In: Trauma: emergency surgery and critical care, JH Siegel, ed. Courtesy of Churchill Livingstone, New York, 1987.)

vomiting, which may increase intracranial pressure or cause laryngospasm or bronchospasm. If topical anesthesia and nerve blocks are used, other problems may be encountered.

3. There is a moderately high probability of damage to the ETT cuff secondary to the marked degree of inflation and manipulations advocated by Gorback.

Oral intubation is a feasible alternative to nasotracheal intubation in the trauma patient with suspected SCI. Oral intubation with a standard laryngoscope and manual in-line axial traction (MIAT), also referred to as manual C-spine immobilization, has been accepted by the American College of Surgeons as part of the Advanced Trauma Life Support protocol for emergency trauma intubation (2,3) (Fig. 1).

Additionally, severely traumatized patients who are hypoxic on arrival at MIEMSS are ventilated continuously by mask with cricoid pressure being applied until intubation is completed. We believe that this approach has prevented further hypoxic insults than can occur during nasal intubation. Cricoid pressure permits positive-pressure ventilation via facemask to reduce the risk of hypoxia while preventing gastric insufflation and regurgitation of stomach contents (4,5). Often, there is not time for the luxury of adequate preoxygenation of an already compromised hypoxic patient with respiratory inadequacy.

We have used this approach for many years (on more than 3000 patients). Approximately 1% of these patients have been diagnosed subsequently to have fractures of the cervical spine. None of them developed any change in the level of spinal cord function during intubation.

In summary, we advise practitioners to be aware of the many risks associated with blind nasal intubation, which is warranted in some clinical situations. Although possibly a

useful "trick," the modifications suggested by Gorbach may magnify those risks and thus should be studied further before being adopted as an acceptable procedure. Our experience in successfully managing the airways of thousands of severely injured trauma patients leads us to advocate the safe and simple technique of oral intubation using MIAT. Also, we stress the concept of continuous ventilation by mask through cricoid pressure.

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Improving the Efficacy of a CPAP System During One-Lung Anesthesia

To the Editor:

Over the years we have read with interest of various devices for administering CPAP to the nondependent lung during one-lung anesthesia for thoracic procedures (1-9).

We would like to share with readers a device we have been using for thoracic cases at our institution for the past 2 years. Since initiating its use, we have not had to use PEEP for the dependent lung, nor have we used a CPAP of more than 7.5 cm H₂O.

When CPAP is being applied, we suggest that a flow of 1 L/min oxygen be provided to the nondependent lung. During one-lung anesthesia, we administer 5 cm H₂O CPAP using a modified Bain circuit (Fig. 1). If Pao₂ decreases intraoperatively, one hand can manually occlude the distal end of the modified Bain circuit (PEEP valve end), while the other hand squeezes the breathing bag, all the time observing the nondependent lung through the surgical incision. Before initiating this procedure, we advise the surgeons because these maneuvers will also inflate the lung on which they are operating. We recommend squeezing the bag of the Bain circuit until blanching of the nondependent lung is readily visible, intermittently providing three to four breaths in conjunction with the above mentioned maneuvers.

A CPAP system such as the one described oxygenates the blood in the nondependent lung with the frequent

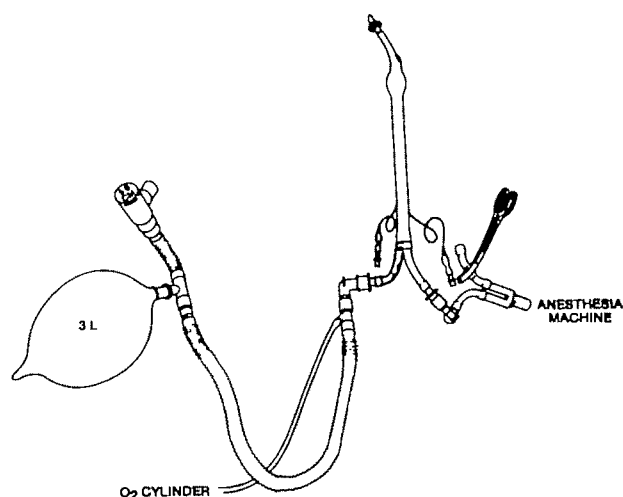


Figure 1. Modified Bain circuit-CPAP System for use during one-lung anesthesia.

manual breaths; at the same time, it may effectively empty the oxygenated blood from the nondependent lung—thus improving the arterial oxygenation. Barotrauma is unlikely to result if the chest is open and the lung deflated before application of this system.

It is important to check to see if blanching of the nondependent lung is not observed, because occasionally blood clots and mucous plugs may prevent inflation of the lung. Simultaneous occlusion of the distal end and squeezing of the breathing bag in the modified Bain circuit should visibly confirm the inflation of the nondependent lung. If inflation does not occur, suctioning and irrigation of the nondependent lung are indicated. Hypoxia during one-lung anesthesia can thus be prevented, just as arterial oxygenation can be improved by decreasing the blood flow in the nondependent lung. Repeated breaths may also assist in overcoming the hypoxic vasoconstrictive reflex in the nondependent lung. We also use this same system during transportation of patients with PEEP. For transportation, we suggest that a flow rate of no less than 8 L/min oxygen be used, and we have found it to be a very useful addition to our armamentarium in such situations.

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Increase in Skin Temperature, By Itself, May Not Indicate Complete Sympathetic Blockade

To the Editor:

In their well thought-out study, Farah and Thomas (1) concluded that tourniquet pain does not involve the sympathetic pathway because stellate ganglion block did not prevent its occurrence. It is possible that the patients in their study did not have complete sympathetic blockade. An increase in skin temperature was used as the evidence of "adequate" sympathetic blockade. An increase in skin temperature, by itself, may not indicate complete sympathetic blockade; temperature may increase with a partial sympathetic blockade (2). After complete sympathetic blockade in patients without peripheral arterial disease, the increase in skin temperature in the upper and lower extremities maybe as little as 0.3°C or as much as 10.5°C (3). Patients with lower temperatures before the block have greater increases than do patients whose baseline temperatures are higher (3,4) because patients attempt to reach 35-36°C, the upper limit of skin temperature in the fingers and toes (5). A person whose temperature is already in this range can, therefore, not have large increases. Abolition of the sympathogalvanic response (SGR) and abolition of sweating are the standard tests of complete sympathetic blockade (6,7). One of these additional tests ought to have been done by Farah and Thomas to assure that the increase in skin temperature they recorded represented complete sympathetic blockade. Because this was not done, the possible role of the sympathetic nervous system in tourniquet pain has not been completely eliminated.

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In Response:

Dr. Benzon's comments are appreciated. In all ten patients whom we studied, the increase in temperature was uniform all across the hand, forearms, and upper arms. Moreover, as discussed in the article, our experience has shown that the duration of increase in temperature in the extremity coincides with the duration of Horner's Syndrome. The continued presence of Horner's Syndrome into the postoperative period was therefore taken as confirmatory evidence of sympathetic block at the time of onset of tourniquet pain. However, we agree with Dr. Benzon that an additional objective test of sympathetic blockade would have absolutely confirmed the presence of complete sympathetic blockade.

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Interscalene Block and Reflex Sympathetic Dystrophy

To the Editor:

We read with interest the recent report by Gillespie et al., "Reflex sympathetic dystrophy: a complication of interscalene block" (1). We question the authors' diagnosis of reflex sympathetic dystrophy (RSD) in this case.

The patient described had an interscalene block for removal of a foreign body in the right middle finger. During performance of the block, a paresthesia was elicited radiating to the thumb. Four days later the patient developed burning pain originating in the shoulder and radiating into the right hand and thumb associated with an area of hyperesthesia over the distal brachial radialis muscle tendon (C₅₋₆ dermatomal distribution). Skin temperatures in the right (36°C) and left (37°C) arms were not significantly different. There was no mention of sweating, edema, or changes in skin color. The patient had complete but transient relief of pain after stellate ganglion block (SGB). Although the SGB was associated with increased skin temperature, it is difficult to have a significant increase in temperature when the baseline temperature is 36°C.

We believe this case does not fit the criteria for RSD. The distribution of pain was clearly dermatomal, whereas RSD pain is usually nondermatomal and generalized in the distal extremity. Pain in RSD typically involves the entire hand or foot and in time may spread to involve the entire extremity (2-4). However, in this case the pain started in the shoulder and radiated to the thumb. There were no signs of sympathetic imbalance noted in this patient, such as changes in vasomotor and sudomotor activity which are seen in RSD (2-4).

A more likely diagnosis for this patient would be post-anesthetic neuralgia. Neuralgia is defined as "pain in the distribution of a nerve or nerves" (5). This case fits this definition. Partial nerve injuries can result in a neuritis, which can manifest as burning pain. Hyperesthesia can also be present. Sympathetic blockade may be useful in preventing sympathalgias in cases of brachial plexalgia (6); therefore, it is possible that the stellate blocks prevented the formation of RSD or causalgia in this case. However, causalgia only occurs in 2.5-5% of peripheral nerve injuries (3). Pain relief from sympathetic block is not specific for RSD or causalgia (7,8). Sympathetic nerve block, by decreasing norepinephrine release, may decrease spontaneous neural firing in damaged nerves (7).

If this case were a true RSD, perhaps more likely etiologies than the interscalene block would have been the foreign body itself or the operation to remove it. These were not discussed as possible causes by the authors. RSD may follow very minor injuries (3).

We have used interscalene block to treat RSD and causalgia with good success. The sympathetic and somatic blockade is useful in providing analgesia for physical therapy (9). We believe that in cases of true RSD, interscalene block is much more likely to be the treatment than the cause.

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To the Editor:

Gillespie et al. (1) recently reported a 70-year-old man who developed reflex sympathetic dystrophy of the right upper extremity after removal of a foreign body lodged in the right middle finger. The surgical procedure was carried out under interscalene brachial plexus block utilizing 3% 2-chloroprocaine. On the tenth postoperative day the patient presented with a constellation of symptoms consistent with a reflex sympathetic dystrophy. The authors attribute the development of the reflex sympathetic dystrophy to either trauma to the brachial plexus by the 22-gauge B-level needle or to neural damage secondary to the 3% 2-chloroprocaine.

Surgical trauma is often cited as a cause of reflex sympathetic dystrophy (2,3). I suggest that the trauma induced by surgical removal of the foreign body would be a more likely trigger of this patient's reflex sympathetic dystrophy relative to above mentioned causes and should be added to the authors' list of potential causes.

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In Response*:

We read with interest the letters by Gibbons et al. and Waldman. After perusing their references we could not help but come to different conclusions.

Although the affected area (of hyperesthesia) did encompass a portion of the distal aspect of two dermatomes, to suggest that the pain was "clearly dermatomal" is unwarranted, at best.

Reflex sympathetic dystrophies have long been described as progressive processes both in terms of signs and symptoms as well as the area of the body involved (1). The duration of each stage is now believed to vary considerably (weeks to years) (2). The absence of some clinical signs and the size of the painful area is not that surprising in view of the timeliness of the patient's presentation.

Although limited, the few post-block neuralgias seen by our pain clinic have been distinctly different in presentation. It is also highly unlikely that the presence and/or removal of a foreign body will produce the described signs and symptoms clearly proximal to the site of the surgery. While it appears that there may be centrally produced phenomena capable of producing peripheral chronic pain

*The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

and hyperpathia (3), we strongly agree with the statement made in the excellent review by Schwartzman and McLellan, "The best diagnostic approach to confirm the presence of RSD is the use of differential neural blockade" (2).

Last, we would like to emphasize that we in no way discounted the role of interscalene blocks in the treatment of RSD. We have employed them in the past, and will continue to use them (in part) for the treatment of upper extremity causalgias in our clinic. We merely point out that in the circumstances described the "treatment" may produce the "injury."

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Another Way to Skin the Catheter

To the Editor:

We read with interest the report of Waldman and Allen (1) regarding the use of Kirschner wires to tunnel intraspinal catheters subcutaneously. We have had similar difficulties in finding the appropriate tunneling devices but have found a different solution.

A long suction tip designed for use in rigid bronchoscopy can be tunneled easily from a small incision in the flank around to the lumbar area. The epidural catheter can then be threaded through the suction tip, the tip removed and the catheter left in place.

To our knowledge the bronchoscopists at our institution do not yet know of this novel use of their equipment. We shall report in a follow-up letter any interesting occurrences arising from this exposition.

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Collodion and Electrocautery Do Not Mix

To the Editor:

Collodion is an ether and alcohol-based solution often used in the closure of pediatric wounds. Readers should be reminded that it is extremely flammable. We recently had a child who had undergone an uncomplicated herniorrhaphy and had collodion applied to the wounds. This done, electrocautery was activated to control a small skin bleeder. Immediately a flash fire resulted in the distribution of the collodion. Although rapidly extinguished with a laparotomy pad, a second degree burn resulted requiring later debridement and grafting.

It is suggested that the electrocautery be removed from the field before the application of collodion because even inadvertent activation of the "Bovie" may result in a significant burn.

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Book Reviews

Key Words in Anesthesiology.

Nicholas M. Greene. New York, Elsevier, 1988, 65 pp.

A system of standardization for anesthesia terminology has long been a goal for academic anesthesiologists. With the introduction of a key word system in the journal *Anesthesiology* in 1974, Dr. Greene began the difficult task of selecting key words which must be precise without being esoteric, and broad without being too general. The system must be capable of being updated, but in such a way that someone starting with a 20-year-old system can add to it, and need not start all over.

Dr. Greene's 3rd Edition, published in book form rather than the previous pamphlet format, demonstrates updating and the need for the same terminology in an everchanging specialty. While the number of key words has not changed drastically since the first edition, the key words added reflect the modernization process. Only five have been added: COMPUTERS, ETHICS, PHARMACODYNAMICS, PUBLICATIONS, and RISK. The number of subheadings has naturally increased with the addition of new complications and drugs. There have been a few minor changes in the terms themselves. For example; EXPLOSIONS has become EXPLOSION, and NEUROMUSCULAR FUNCTION has become NEUROMUSCULAR JUNCTION.

This reviewer's only criticism with *Key Words in Anesthesiology* is that the system should be more closely aligned with the MEDLARS system of key words. This would permit the system to be used for access into a rapid retrieval system as well as for a filing system. In this case, the difference between using the Medlars term, ANESTHESIA, INTRAVENOUS as opposed to ANESTHETICS, INTRAVENOUS, will allow a more expedient search of the literature. It is hoped that future editions will address this issue.

Overall Dr. Greene's *Key Words in Anesthesiology* provides an excellent basic filing system for the field and is recommended as a starting point for anyone trying to develop a home filing system in this specialty. More important, authors would be well advised to use it as a reference in selecting the appropriate key words when preparing their manuscripts.

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History of Blood Gas Analysis. Vol. 25, No. 4, International Anesthesia Clinic

Severinghaus SW and Astrup SP. Boston: Little, Brown, 1987, 224 pp, \$20.00 for single issue and \$50.00 for four issues.

This charming review of blood gas analysis has the twin virtues of being both scholarly and readable. This is no dry-as-dust simple recounting of advances made by faceless people doing their work in a vacuum. Rather, it tells the story of flesh-and-blood people working in the real environment of their times. It is not often that one comes away from an historic volume with such a sense of who the people were who (often literally with their own hands) created apparatus which we take for granted today. To paraphrase another expression, this excellent monograph is about blood gas analysis with a human face. This is all made concrete by photographs of these pioneers that give the reader a glimpse into the features if not the personality of these men, one that is not otherwise available.

The volume is divided into eight sections. The first three are devoted to electrochemistry, acid-base balance and CO₂ tensions, the next three to oxygen measurements and the Clark electrode, and the final two to oximetry and pulse oximetry. The first two subjects have been reviewed repeatedly elsewhere. However, the presentation of Hasselbalch's "reduzierte pH" is particularly welcome to this reviewer because it is a concept that is both very important and usually ignored. The section on CO₂ tension is both comprehensive and balanced. It is not to detract from the ingenuity of Richard Stow, working at the Mayo Clinic in 1952 under Earl Wood, to point out that his failure to understand the role of collision broadening in the Luft infrared gas detector led to his failure to create a workable device for measuring CO₂ in the gas phase.

The treatment of Kurt Kramer, who worked in oximetry, requires reevaluation. The authors are formally correct in their description of him. As they state, he was a physiologist in prewar Germany and worked on oximetry before and during the war for the Luftwaffe. He was also a concert pianist and wrote about Bach. They quote Zijlstra, a prominent Dutch investigator, who described him as "ein gebildeter Mensch," a cultivated individual. But the authors relegate to a footnote—and without comment—that he had also been a member of the SS and had been interviewed in that capacity by Earl Wood in 1946 in a POW camp. Recall that one had to volunteer to become a member of the SS, the organization of the elite group of supporters of the

Third Reich. To describe someone as a member of the SS is one of the strongest condemnations one can make of that individual. It is important today to be clear about the errors of the past or else, in Sanatayana's words, we shall be condemned to repeat them.

This volume is particularly strong in the description of the oxygen electrode now known as the Clark electrode and the variations that it spawned. The extension from the measurements of O₂ to the CO₂ measurement device that bears Severinghaus' name is well described. He also gives full credit to Stow's prior efforts. The final sections on oximetry and pulse oximetry provided this reviewer with the greatest amount of fresh information. The details of the Japanese phase of the story are fascinating.

This beautifully crafted book has less than the usual share of minor difficulties and typos. Bronk, not Brink, was the first President of Rockefeller University. The name of the city Kiel is misspelled Keil. Some of the bibliographic

reference numbers are incorrect. The observers in the study of Comroe and Botelho were far from "keen." During the War, E.D. Adrian was merely Sir Adrian. His elevation to Lord—and later to Baron—occurred long after the war.

For anyone interested in the development of methods for blood gas analysis—and this must include many in anesthesia—this book is a must. It is rare that a topic is covered so well by including letters from the active "players" in the game, and that provides an authenticity infrequently seen in historic summaries.

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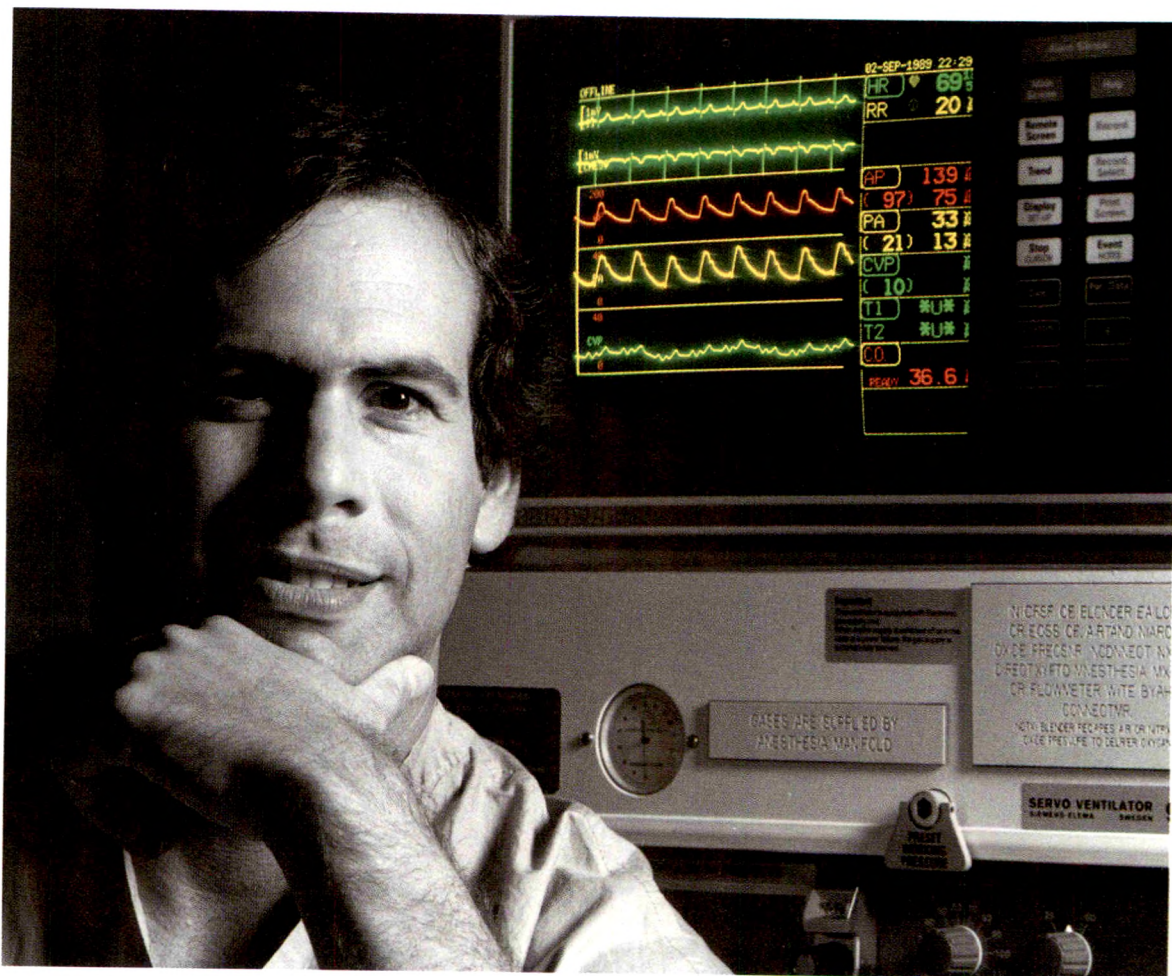
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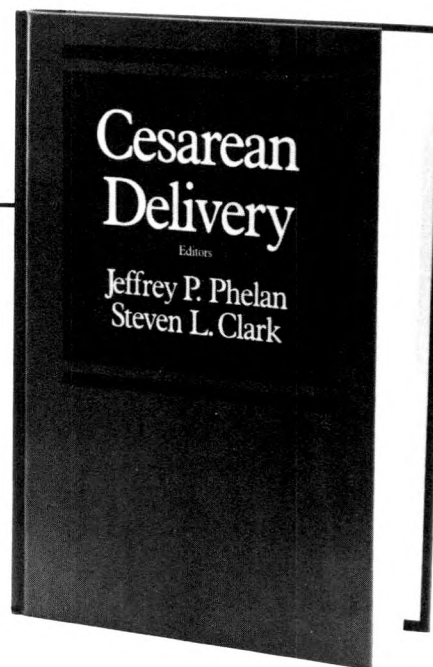
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Editorial

Glimpses of the Past

Nicholas M. Greene, MD

Key Words: Historical Notes—editorial

This issue of “A and A” marks the inauguration of a series of brief abstracts that we will call **Historical Notes**. We hope these historical notes will serve to encourage and contribute to an even greater rate of increase in interest in that new but rapidly growing subspecialty in anesthesiology, the history of our specialty. The burgeoning membership of the relatively recently established Anesthesia History Association in the United States and the History of Anaesthesia Society in Britain, together with the success of the Second International Symposium on the History of Anaesthesia held last summer in London at the Royal College of Surgeons of England, are but a few of the many indications of the growing recognition among anesthesiologists that our specialty has a rich and interesting historical heritage, a heritage worth knowing about.

Historical notes will be brief, a bit shorter, by and large, than the average letter to the editor. One, two, or three will be found in each issue. They will occupy the otherwise empty space remaining when an article

ends at the top of a page. The table of contents will list the pages on which historical notes appear.

All historical notes will be drawn from historically noteworthy articles published 50 or more years ago in *Anesthesia and Analgesia* or, as then known, *Current Researches in Anesthesia and Analgesia*. Given that number 1 of volume 1 of the journal appeared in 1922, the material gleaned from issues between 1922 and 1938, or so, will provide information about an era of great importance in anesthesia, but an era about which many of today's anesthesiologists are ignorant. Many, if not most, histories of anesthesia emphasize events that took place in the 19th Century to the near exclusion of more recent happenings. It was between 1922 and 1940, however, that the foundations of modern anesthesiology, how it is now organized and how it is now practiced, were first established.

Because *Anesthesia and Analgesia* was one of only two anesthesia journals published between 1922 and 1940, and the only one published in North America, its pages will prove to be a particularly valuable source of information about the formative years of anesthesiology.

Nicholas M. Greene, MD

Hemodynamic Profiles of Prostaglandin E₁, Isoproterenol, Prostacyclin, and Nifedipine in Vasoconstrictor Pulmonary Hypertension in Sheep

Richard C. Prielipp, MD, Myer H. Rosenthal, MD, and Ronald G. Pearl, MD, PhD

PRIELIPP RC, ROSENTHAL MH, PEARL RG.

Hemodynamic profiles of prostaglandin E₁, isoproterenol, prostacyclin, and nifedipine in vasoconstrictor pulmonary hypertension in sheep. *Anesth Analg* 1988;67:722-9

Patients with pulmonary hypertension challenge the anesthesiologist with complex alterations of hemodynamic function. To study the effects of multiple therapeutic interventions, a stable model of pulmonary hypertension in sheep was developed using continuous infusion of the vasoconstrictor U46619, a thromboxane A₂-mimetic. The pulmonary and systemic effects of four pulmonary vasodilators (prostaglandin E₁, isoproterenol, prostacyclin, and nifedipine) were compared at doses producing equivalent reduction in systemic blood pressure. Although all four drugs decreased pulmonary artery pressure and resistance, distinct differences in drug hemodynamic profiles were found. Prostaglandin E₁ and isoproterenol demonstrated the greatest pulmonary specificity, increased cardiac output significantly, and decreased pulmonary vascular resistance. Prostaglandin E₁ produced the largest decrease in pulmonary

artery pressure (from 31 ± 1 to 22 ± 2 mm Hg). Isoproterenol markedly increased heart rate (from 119 ± 6 to 182 ± 10 beats/min) and resulted in significant dysrhythmias that necessitated limiting infusion of this drug; isoproterenol did not affect stroke volume. Prostacyclin demonstrated intermediate pulmonary specificity and produced the largest increase in cardiac output (from 1.7 ± 0.2 to 3.1 ± 0.3 L/min). Nifedipine exhibited the least pulmonary specificity and was the least effective agent in decreasing pulmonary artery pressure. In this model different pulmonary vasodilators exerted different hemodynamic effects, suggesting that appropriate drug selection for treatment of pulmonary hypertension should depend on baseline heart rate and rhythm, pulmonary artery pressure, systemic artery pressure, arterial oxygenation, and cardiac output.

Key Words: LUNG, BLOOD FLOW—pulmonary hypertension. HORMONES, PROSTAGLANDINS—prostacyclin. PHARMACOLOGY—nifedipine. HEART—*isoproterenol*.

Pulmonary hypertension with associated right ventricular dysfunction remains a therapeutic problem. Clinical use of vasodilators for therapy of pulmonary hypertension has yielded inconsistent results (1). Potential complications of vasodilator therapy may include systemic hypotension, right ventricular ischemia, arrhythmias, exacerbation of pulmonary hypertension, and arterial oxygen desaturation (2,3). Active pulmonary vasoconstriction is a significant component of the increased vascular resistance in both acute and chronic pulmonary hypertension (4).

Supported in part by a grant from the Society of Cardiovascular Anesthesiologists.

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A drug with preferential pulmonary (versus systemic) vasodilator activity would minimize the risk of systemic complications while effectively lowering pulmonary resistance. Clinical studies evaluating pulmonary vasodilators are often conflicting due to small numbers of patients and the heterogeneity of drug response accompanying human pulmonary hypertension. Extensive human comparative studies are not feasible. We have therefore developed a method for producing sustained pulmonary hypertension in vivo by utilizing continuous infusion of 9,11-dideoxy-11 α ,9 α -epoxymethano-prostaglandin F₂ α (U46619) in sheep. This method enabled us to compare the vasodilator effects of four drugs selected on the basis of 1) favorable reports suggesting clinical efficacy in pulmonary hypertension (5-18), 2) activation or blockade of various receptors and 3) effective duration of action. Prostaglandin E₁ (PGE₁) is a short-acting lino-

lenic acid derivative that activates adenylate cyclase and increases intracellular cyclic AMP levels (19). Isoproterenol is a potent short-acting sympathomimetic amine with activity at B_1 and B_2 receptors. Prostacyclin (PGI_2), an endogenous cyclooxygenase derivative of arachidonic acid, has a short half-life and may act via the cyclic AMP pathway (20). PGI_2 is currently the only arachidonic acid metabolite that demonstrates pulmonary vasodilator activity (21) and may help modulate intrinsic vascular tone in the lung (22,23). Nifedipine is a long-acting slow-channel calcium antagonist generally administered via the oral or sublingual route.

Methods

The protocol for this study was approved by the Stanford Panel on Laboratory Animal Care.

Protocol

Nine sheep weighing 19–29 kg were anesthetized with thiopental 20 mg/kg IV, intubated, and mechanically ventilated at a tidal volume of 15–25 ml/kg, with a rate adjusted to maintain arterial carbon dioxide tension between 35 and 45 mm Hg. Anesthesia was maintained with halothane (end-tidal 1%) in oxygen. Temperature was maintained at 37.5–39°C with a warming blanket as needed. After induction of anesthesia, systemic arterial, central venous, and triple-lumen pulmonary arterial catheters were placed by peripheral cutdown. Heart rate was measured by continuous ECG monitoring. Twenty minutes after catheter placement, we obtained baseline measurements. Recorded hemodynamic variables included heart rate (HR), mean systemic arterial pressure (SAP), central venous pressure (CVP), mean pulmonary artery pressure (PAP), pulmonary artery occlusion pressure (PAOP), and cardiac output (CO). Samples for arterial and mixed venous blood gas analyses were obtained. Pulmonary hypertension was induced by continuous intravenous infusion of the vasoconstrictor U46619, initially adjusting the infusion rate until a PAP exceeded 30 mm Hg and CO was reduced by at least 25%; the infusion rate was then maintained constant for the duration of the experiment. Hemodynamic measurements were obtained 30 minutes later. PGE_1 , isoproterenol, and PGI_2 were then administered in random order as continuous drug infusions titrated until SAP was reduced to 70% of each predrug value or HR increased to 150% of the predrug rate. We obtained

hemodynamic and blood gas measurements before each drug infusion and 15 minutes after establishing a stable infusion rate. A 45-minute stabilization and washout period was allowed between drugs. Forty-five minutes after the third randomized drug, nifedipine was administered as a continuous intravenous infusion titrated to produce a 30% reduction in SAP; data were collected 15 minutes later.

Measurement Techniques

Intravascular pressures were measured at end-expiration with Hewlett-Packard quartz transducers (model 1290A) referenced to the left atrial level and recorded on a Hewlett-Packard eight-channel recorder. Cardiac output was determined in triplicate by the thermodilution technique, using 10 ml of room-temperature saline injectate and an Edwards 9520A cardiac output computer. Blood gas tensions were analyzed using a Corning 168 pH/blood gas analyzer. Venous and arterial oxygen saturations were calculated with a Severinghaus slide rule (24), assuming a P_{50} value of 27 mm Hg for sheep hemoglobin (25). Oxygen content (Co_2) was calculated as: $Co_2 = (1.34 \times Hgb \times So_2) + (0.003 \times Po_2)$. Shunt fraction (Qs/Qt) was calculated as: $(\text{capillary oxygen content} - \text{arterial oxygen content}) / (\text{capillary oxygen content} - \text{mixed venous oxygen content})$. Pulmonary vascular resistance (R_p) was calculated as $(PAP - PAOP) \times 80/CO$; systemic vascular resistance (R_s) as $(SAP - CVP) \times 80/CO$; and stroke volume (SV) as CO/HR . The R_p/R_s ratio was calculated to assess the balance of pulmonary to systemic vasodilator effects.

Drugs

Prostaglandin E_1 , PGI_2 , and U46619 were gifts from Doug McCarter of Upjohn Diagnostics, Kalamazoo, Michigan. PGE_1 was prepared in 0.2 M phosphate buffer at a concentration of 0.25 mg/50 ml. PGI_2 was dissolved directly in 0.05 M Tris buffer (pH 9.4). The U46619 stock solution was prepared in absolute alcohol (concentration 5 mg/ml) and stored at -10 to -20°C ; aliquots of 0.4 ml were diluted in 50 ml normal saline and infused with a Harvard pump for study administration. Nifedipine (Pfizer, Groton, Connecticut) was prepared by dissolving 25 mg in a solution of 15 g polyethylene glycol 400 and 15 g absolute ethanol dissolved in 0.9% saline (total volume of 50 ml). Aluminum foil was used for light shielding throughout the preparation and administration of nifedipine.

Table 1. Hemodynamic Variables Related to Time

Time	HR (beats/min)	Mean SAP (mm Hg)	Mean PAP (mm Hg)	CO (L/min)	Rp (dynes·sec·cm ⁻⁵)	Rs (dynes·sec·cm ⁻⁵)
Baseline	132 ± 8	98 ± 5	12.5 ± 1.0	2.82 ± 0.17	195 ± 23	2717 ± 213
30'-U46619	115 ± 4*	123 ± 3†	29.3 ± 1.3†	1.72 ± 0.09†	1036 ± 86†	5543 ± 288†
Predrug 2	119 ± 5	119 ± 3†	30.2 ± 1.4†	1.85 ± 0.20†	1057 ± 137†	5294 ± 498†
Predrug 3	119 ± 6	118 ± 4†	31.4 ± 1.2†	1.56 ± 0.12†	1265 ± 123†	6227 ± 742†
Predrug 4	113 ± 3*	108 ± 4*	31.1 ± 1.1†	1.60 ± 0.13†	1201 ± 106†	5528 ± 692†

Values are means ± SEM for nine time points.

**P* < 0.05 compared to baseline; the 30'-U46619 and predrug 1 time points are identical.

†*P* < 0.01.

Abbreviations: HR = heart rate; SAP = mean systemic arterial pressure; PAP = mean pulmonary pressure; CO = cardiac output; Rp = pulmonary vascular resistance; Rs = systemic vascular resistance.

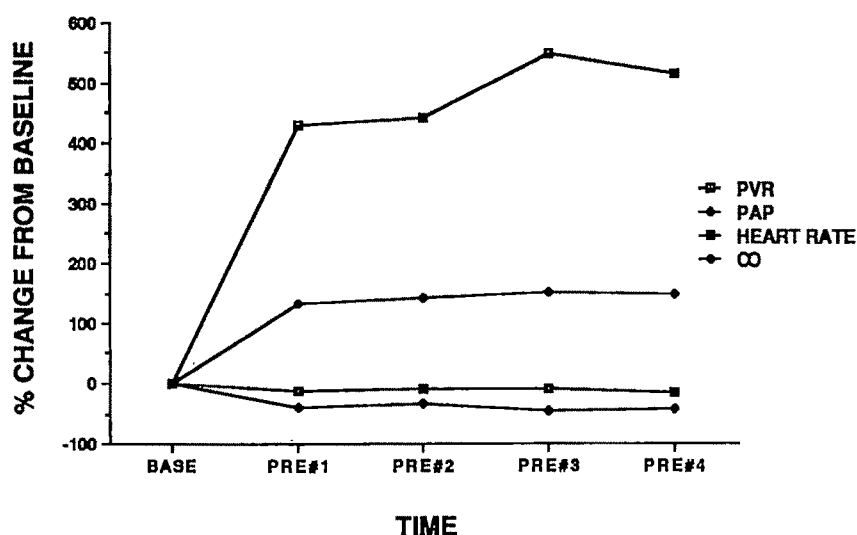


Figure 1. Percent change in pulmonary vascular resistance (PVR), in pulmonary artery pressure (PAP), in heart rate, and in cardiac output (CO), after the administration of the thromboxane A₂-mimetic U46619.

Statistical Analysis

The effects of U46619 infusion and the stability of the model over the 3-4-hour drug study period were assessed by one-way repeated measures analysis of variance (ANOVA) of five time points. The time points were baseline, 30 minutes of U46619 infusion (before infusion of the first drug), and the three other predrug times (second drug, third drug, and fourth drug, in order). Duncan's multiple range comparison test was used to identify differences between time points. Changes among drug effects were analyzed by a one-way repeated measures ANOVA using the change in value during drug therapy. Probability values less than 0.05 were considered significant. Results are reported as mean values ± SEM.

Results

U46619, infused at a rate of $1.1 \pm 0.1 \mu\text{g} \cdot \text{Kg}^{-1} \cdot \text{min}^{-1}$, increased PAP 157%, increased Rp 500%, increased Rp/Rs 205%, and decreased CO 35%. These changes

remained stable throughout the study (Table 1, Fig. 1). Baseline arterial Po₂ averaged 516 ± 10 mm Hg and decreased 17% by 30 minutes after U46619 infusion; hypoxemia did not occur during drug therapy (Table 2). Average drug infusion rates were $0.8 \pm 0.2 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for PGE₁, $23 \pm 6 \text{ ng} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for isoproterenol, $0.8 \pm 0.3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for PGI₂, and $11 \pm 3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for nifedipine. SAP decreased approximately 30% with PGE₁, PGI₂, and nifedipine (*P* < 0.01) but did not change significantly with isoproterenol (Table 3); instead, tachycardia and arrhythmias limited isoproterenol infusion. PAP and Rp decreased significantly with all four drugs (Fig. 2). PGE₁ reduced PAP significantly more than nifedipine, isoproterenol, and PGI₂. All four drugs produced equivalent decreases in Rp. The Rp/Rs ratio remained unchanged with PGE₁ or isoproterenol but increased with both PGI₂ and nifedipine. The increase with nifedipine was significantly greater than with isoproterenol (*P* < 0.01), PGE₁ (*P* < 0.01), or PGI₂ (*P* < 0.05). CO increased with all four drugs; the increase with PGI₂ was significantly greater (*P* < 0.05)

Table 2. Oxygenation Variables Related to Drug Therapy

Drug	Arterial O ₂ (mm Hg)	Venous O ₂ (mm Hg)	Qs/Qt Shunt (%)
Pre PGE ₁	422 ± 49	42.6 ± 2	17.1 ± 4.3
Post PGE ₁	433 ± 50	59.1 ± 6*	23.5 ± 4.5†
Pre ISO	416 ± 36	49.6 ± 2	17.6 ± 2.1
Post ISO	462 ± 31*	71.2 ± 3†	23.3 ± 2.2†
Pre PGI ₂	442 ± 38	49.5 ± 2	16.1 ± 2.6
Post PGI ₂	464 ± 35	67.9 ± 3†	23.0 ± 2.1†
Pre NIF	365 ± 50	42.4 ± 3	19.0 ± 3.9
Post NIF	399 ± 49*	62.5 ± 6†	24.7 ± 2.7*

Values are means ± SEM for nine sheep.

* $P < 0.05$ compared to predrug value.

† $P < 0.01$ compared to predrug value.

Abbreviations: PGE₁ = prostaglandin E₁; ISO = isoproterenol; PGI₂ = prostacyclin; NIF = nifedipine.

than with nifedipine. SV increased 47% with PGE₁, 48% with PGI₂, and 43% with nifedipine, but was unchanged by isoproterenol. The effect of isoproterenol on SV was significantly different ($P < 0.05$) from the other three drugs. HR increased with isoproterenol and PGI₂ but did not significantly change with nifedipine or PGE₁. The increase with isoproterenol was significantly different ($P < 0.01$) from the response to the other three drugs. The increased HR with PGI₂ was significantly different only from PGE₁ ($P < 0.05$). Nifedipine did not affect CVP or PAOP, whereas both PGE₁ and PGI₂ significantly decreased these pressures. Isoproterenol decreased PAOP but had no significant effect on CVP. Shunt fractions and mixed venous Po₂ were increased equally by all four drugs (Table 2).

Discussion

Pulmonary hypertension may develop secondary to complex vasoconstrictive and structural changes in pre- and postcapillary units of the pulmonary vascular bed. Active vasoconstriction exists in mitral stenosis, adult respiratory distress syndrome (26), pulmonary embolism (27), hypoxia (28), primary pulmonary hypertension, and other diseases. Components of certain anesthetic techniques (nitrous oxide, ketamine) or stress incurred in the operating room (hypothermia, elevated catecholamines) may potentiate pulmonary hypertension and adversely affect right ventricular function (29–31). An ideal pulmonary vasodilator for the treatment of pulmonary hypertension and associated right ventricular dysfunction should decrease pulmonary artery pressure and pulmonary vascular resistance, increase cardiac output, and not worsen lung ventilation-perfusion matching. We designed this study to evaluate the comparative vasodilator responses of four drugs during vasoconstrictor pulmonary hypertension.

The stable endoperoxide thromboxane A₂-mimetic U46619 has previously been reported to cause pulmonary hypertension in sheep with little effect on the systemic circulation (32). Thromboxane A₂ is implicated as a mediator of pulmonary hypertension and hypoxemia during experimental intravascular complement activation in sheep (33); a component of thromboxane A₂-induced pulmonary hypertension may be modulated via platelet aggregation (34). Potent aggregating effects on platelet function as well as vascular smooth muscle contractility are exhibited by U46619 (35,36). Other evidence demonstrates U46619 to be a dose-dependent modulator of thromboxane metabolism in the perfused guinea pig lung (37,38) and may alter the metabolic fate of other prostenoids in the pulmonary endothelium. In early septic shock in humans, levels of thromboxane B₂ (the stable degradation product of thromboxane A₂) are significantly correlated with an elevated pulmonary vascular resistance and an elevated alveolar-to-arterial oxygen gradient (39). Infusion of U46619 in this study induced sustained pulmonary hypertension without excessively increasing systemic arterial pressure. Elevations in PAP and Rp remained stable throughout the 4-hour study period. Vasodilator drug infusion significantly reduced pulmonary artery pressure and increased cardiac output, indicating that reversible pulmonary vasoconstriction was present. The U46619 infusion therefore represents an appropriate situation to examine the vasodilator properties of these drugs.

Pulmonary vasodilator therapy may be complicated by arterial oxygen desaturation and increased pulmonary shunt (40). In our study, although drug therapy with PGE₁, isoproterenol, PGI₂, and nifedipine significantly increased shunt fraction, there were no significant changes in arterial oxygen tension (Table 2). All four vasodilators markedly increased CO and mixed venous oxygen tensions. Lynch et al. (41) demonstrated that shunt fraction varied directly with the mixed venous oxygen tension in a canine model of oleic acid-induced lung injury. Sandoval et al. (42), studying the effects of hydralazine on shunt in a similar canine model, speculated that the increased mixed venous oxygen tension accompanying hydralazine therapy blocked the hypoxic pulmonary vasoconstriction that would normally limit perfusion to low ventilation areas. These studies help explain why drugs that cause large increases in CO may also result in large increases in calculated shunt fraction.

Pulmonary vasodilator therapy may be complicated by systemic hypotension (1). Vlahakes et al. (43) studied right coronary blood flow in dogs with acute right ventricular hypertension (produced by pulmonary artery constriction) and demonstrated

Table 3. Hemodynamic Variables Related to Drug Therapy

Drug	HR (beats/min)	Mean SAP (mm Hg)	Mean PAP (mm Hg)	CO (L/min)	Rp (dynes-sec-cm ⁻⁵)	Rs (dynes-sec-cm ⁻⁵)	Rp/Rs
Pre-PGE ₁	116 ± 5	121 ± 3	30.9 ± 1.5	1.5 ± 0.1	1276 ± 137	6317 ± 685	0.202 ± 0.016
Post-PGE ₁	126 ± 4	87 ± 2†	22.0 ± 1.7*	2.4 ± 0.2†	614 ± 82†	2980 ± 282†	0.206 ± 0.016
Pre-ISO	119 ± 6	121 ± 4	29.8 ± 1.2	1.8 ± 0.1	996 ± 90	5108 ± 403	0.195 ± 0.014
Post-ISO	182 ± 10†	110 ± 6	24.6 ± 1.7†	3.2 ± 0.2†	513 ± 55†	2617 ± 180†	0.196 ± 0.021
Pre-PGI ₂	118 ± 4	118 ± 3	30.1 ± 0.9	1.7 ± 0.2	1085 ± 90	5371 ± 446	0.202 ± 0.009
Post-PGI ₂	145 ± 8†	85 ± 2†	25.2 ± 1.8*	3.1 ± 0.3†	570 ± 90†	2336 ± 195†	0.244 ± 0.023*
Pre-NIF	113 ± 3	108 ± 4	31.1 ± 1.0	1.6 ± 0.1	1200 ± 100	5263 ± 692	0.228 ± 0.017
Post-NIF	123 ± 9	74 ± 3†	28.9 ± 0.9†	2.4 ± 0.3*	810 ± 110†	2523 ± 323†	0.321 ± 0.023†

Values are means ± SEM for nine sheep.

*P < 0.05 compared to predrug value.

†P < 0.01.

The abbreviations as in Tables 1 and 2.

Rp/Rs = ratio of pulmonary to systemic resistance.

that right ventricular free wall ischemia precipitated acute right ventricular failure. Infusion of the vasoconstrictor phenylephrine restored myocardial perfusion pressure and "coronary driving pressure" by raising aortic pressure and reversed right ventricular failure. A drug with *preferential* pulmonary vasodilator effect minimizes the risk of systemic hypotension, which can result in coronary ischemia and acute right ventricular failure. In our study, the specificity of pulmonary vasodilation was assessed by the change in Rp/Rs ratio with drug therapy. An ideal pulmonary vasodilator would reduce Rp as much or more than Rs, thereby decreasing this ratio during drug infusion. None of the vasodilators demonstrated this ideal selectivity for pulmonary smooth muscle vasculature either in our study or in clinical use.

Our data suggest distinct hemodynamic profiles among the four drugs studied in this vasoconstrictor model of pulmonary hypertension. Isoproterenol, one of only two drugs that did not change the Rp/Rs ratio, resulted in large increases in CO while simultaneously decreasing PAP and Rp; isoproterenol was the only drug that did not increase stroke volume. Because isoproterenol maintained SAP in our study, tachycardia limited its infusion (according to protocol). Clinically, isoproterenol infusions may be limited by tachycardia, palpitations, and tremulousness (16), although careful administration along a dose-response curve may allow more optimal titration. Isoproterenol-induced increases in HR and CO and decreases in Rp have been consistently found in clinical and animal studies (16,44-47). PAP was decreased in some (46,47) but not all studies (16,45). Molloy et al. (46) found isoproterenol ineffective in a canine pulmonary embolism model, however, because its direct inotropic effect was more than offset by its peripheral vasodilating effect. All their isoproterenol-treated animals died. These authors caution

against isoproterenol infusion in the setting of low baseline systemic blood pressure. Chronic or prolonged treatment with a β -agonist will induce pharmacologic tolerance due to down regulation of β -receptors, and loss of therapeutic responsiveness has been observed in the chronic setting.

PGE₁ did not change the Rp/Rs ratio and resulted in the largest decrease in PAP of any agent studied. Cardiac output increased 43% and Rp decreased 45%. PGE₁ has generated interest because endogenous prostaglandins may contribute to the physiologic regulation of pulmonary blood flow, and some have postulated that a deficiency of endogenous prostaglandins causes primary pulmonary hypertension (20,48). PGE₁ has marked pulmonary clearance due to 15-hydroxyprostaglandin dehydrogenase in the lungs (49,50). Rapid pulmonary clearance of PGE₁ may decrease the active drug concentration in the systemic circulation and contribute to its relative selectivity as a pulmonary vasodilator. Metabolism, however, may be altered in abnormal or diseased lungs (51).

Recent reports indicate the effectiveness of PGE₁ as a pulmonary vasodilator. We previously compared PGE₁, nitroglycerin, sodium nitroprusside, and hydralazine in vasoconstrictor (U46619) pulmonary hypertension in sheep and found PGE₁ to demonstrate the greatest pulmonary specificity and potency (52). Clinical applications utilizing PGE₁ are now being reported. Szczeklik et al. (11) studied PGE₁ infusion in 20 patients with pulmonary hypertension secondary to mitral valve disease. PAP decreased 24%, CO increased 13%, and pulmonary resistance decreased 33%. D'Ambra et al. (53) treated five patients with refractory right heart failure and severe pulmonary hypertension in the immediate postcardiopulmonary bypass period by using central venous infusion of

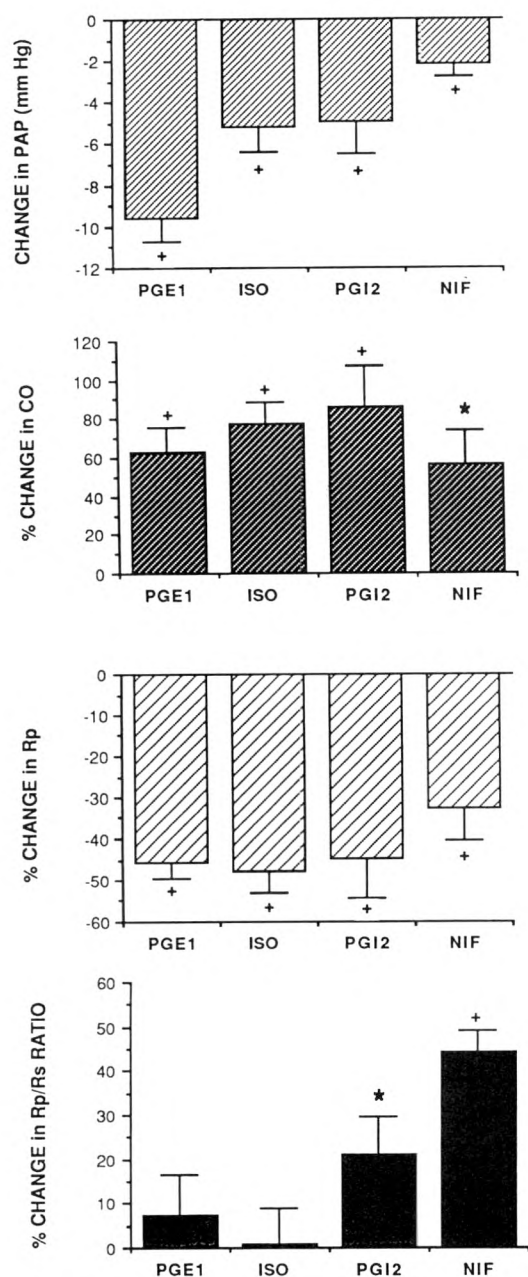


Figure 2. Change in mean pulmonary artery pressure (PAP) and percentage change in cardiac output (CO), in pulmonary vascular resistance (Rp), and in the ratio of the pulmonary to systemic vascular resistance (Rp/Rs) with the administration of prostaglandin E₁ (PGE₁), isoproterenol (ISO), prostacyclin (PGI₂), and nifedipine (NIF). Each value represents the mean \pm SEM of nine sheep. * $P < 0.05$ compared to predrug value. + $P < 0.01$ compared to predrug value. See text for comparison between different drugs.

PGE₁ and left atrial infusion of norepinephrine. Rp decreased 85%, and all five patients survived.

In our study, prostacyclin (PGI₂) significantly increased (worsened) the Rp/Rs ratio. PAP and Rp decreased, while CO greatly increased. PGI₂, an arachidonic acid metabolite normally produced in vascular endothelial cells (54), may be a spontaneous

modulator of vascular tone in the lung (23). Bush et al. (55) reported that PGI₂ caused dose-dependent pulmonary vasodilation in 20 children with pulmonary hypertension secondary to congenital heart disease. Within the dose utilized ($5\text{--}20\text{ ng}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$), no significant changes occurred in the Rp/Rs ratio. Systemic hypotension did follow a higher dose range. Flushing, headache, nausea, and vomiting are common side effects of PGI₂ (56). Rubin et al. found that these effects limited PGI₂ infusion in four of seven patients (57).

In our study, nifedipine demonstrated the least favorable hemodynamic profile in two respects: it produced the smallest decrease in PAP and the largest increase in the Rp/Rs ratio. Clinical experience with the calcium-channel blocking drugs has been inconsistent. Of the currently available calcium-channel blocking drugs, nifedipine appears to have the greatest pulmonary selectivity and the greatest effect on pulmonary vasculature (13), especially in patients demonstrating preexisting Raynaud's phenomenon (58). Rubin et al. (15) reported on nine patients treated with nifedipine for primary pulmonary hypertension; PAP did not change, CO increased, and Rs and Rp decreased. These changes were consistent during later follow-up. Rich et al. (17) studied nifedipine in seven patients with primary pulmonary hypertension and found a significant reduction in PAP; however, five of seven patients had an unfavorable increase in the Rp/Rs ratio. Other authors have reported failure of nifedipine therapy in primary pulmonary hypertension (59,60). Packer et al. (3) reported that nifedipine and verapamil exert detrimental negative inotropic effects on the right ventricle. Cardiac output did not change with nifedipine and was decreased with verapamil. One patient treated with verapamil sustained marked hypotension and suffered cardiac arrest. It is unclear whether the acute intravenous administration of nifedipine as in our study potentiated the negative inotropic effect of this drug.

In summary, we have developed a stable pulmonary hypertension model utilizing the vasoconstrictor U46619 in sheep. Four vasodilators were examined to determine their potency and relative specificity for the pulmonary vasculature. Prostaglandin E₁ and isoproterenol were the most selective pulmonary vasodilators. PGE₁ also resulted in the largest decrease in pulmonary artery pressure. Isoproterenol infusion was frequently complicated by tachycardia and arrhythmias. PGI₂ was intermediate in pulmonary selectivity while markedly increasing cardiac output. Nifedipine demonstrated the least favorable pulmonary Rp/Rs profile with systemic vasodilator

activity significantly more potent than pulmonary vasodilator activity. The limited clinical experience with pulmonary vasodilator therapy is consistent with our experimental findings. The four vasodilators examined in this study demonstrate significantly different hemodynamic drug profiles. Prostaglandin E_1 appears to have the most favorable hemodynamic vasodilator profile in experimental U46619-induced pulmonary hypertension in sheep. Drug selection for clinical application may vary depending on baseline hemodynamic parameters such as heart rate and rhythm, systemic and pulmonary arterial pressure, arterial oxygenation, and baseline cardiac output.

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Cardiovascular Effects of Fentanyl Reversal by Naloxone at Varying Arterial Carbon Dioxide Tensions in Dogs

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MILLS CA, FLACKE JW, MILLER JD, DAVIS LJ, BLOOR BC, FLACKE WE. Cardiovascular effects of fentanyl reversal by naloxone at varying arterial carbon dioxide tensions in dogs. *Anesth Analg* 1988;67:730-6.

Clinical reports, as well as animal studies, have described cardiovascular and sympathetic stimulation after the administration of naloxone (NX) to reverse opioid-induced respiratory depression. This investigation examines the effect of P_{aCO_2} on hemodynamic and adrenergic responses to NX, by means of 24 experiments carried out in six dogs. Each dog underwent NX reversal of fentanyl (FEN) at three different P_{aCO_2} levels: 20, 35, and 60 mm Hg. In a final series of six experiments, the dogs were exposed to increasing P_{aCO_2} after autonomic block by total spinal anesthesia and vagotomy. During enflurane anesthesia, 50 $\mu\text{g/kg}$ FEN decreased mean arterial blood pressure (MAP), heart rate (HR), and plasma concentrations of norepinephrine (NE) and epinephrine (EPI) significantly. NX 0.4 mg promptly returned HR and MAP to baseline or above in all experiments; catecholamine (CA) levels increased only in hyper-

capnic dogs. Increases in HR were the same in all series. MAP, EPI, and NE levels were significantly greater than pre-FEN baseline values only in hypercapnic dogs 1 minute after NX and were also significantly higher in hypercapnic than in hypocapnic dogs at this time. NE levels were greater in hypercapnic dogs at all time periods after NX. In blocked dogs, neither F nor NX had any effects on hemodynamic functions or plasma CA levels; the institution of hypercapnia caused significant decreases in HR, MAP, and systemic vascular resistance. This direct circulatory depressant action of an elevated P_{aCO_2} may have attenuated the indirectly mediated excitatory hemodynamic effects of NX in intact dogs, thus explaining the relatively greater effect of hypercapnia on adrenergic than on hemodynamic responses to reversal. This study suggests that abrupt increases in blood pressure and plasma CA levels after naloxone can be blunted if normocapnia or hypocapnia is established before naloxone administration.

Key Words: ANTAGONISTS, NARCOTIC—naloxone. ANESTHETICS, INTRAVENOUS—fentanyl. ANALGESICS—fentanyl.

Residual effects of intraoperative narcotics on respiratory control may result in postoperative hypoventilation and hypercapnia. The pure narcotic antagonist, naloxone, is used frequently to reverse this respiratory depression. Unfortunately, the use of naloxone may be associated with excessive cardiovascular stimulation (1-6). There have been sporadic reports of untoward circulatory events, ranging from severe hypertension (1) to cardiac arrhythmias (1,5), pulmonary edema (3,7-9), and death (10). Various explanations have been given for this cardiovascular stimulation, including an acute narcotic withdrawal

syndrome (11), antagonism of analgesia, and sudden awakening (12) with the resultant rapid normalization of previously narcotized autonomic regulatory processes (13,14). However, even in deeply anesthetized dogs, reversal of fentanyl with naloxone causes the sudden return of blood pressure, heart rate, and cardiac output to values sometimes greater than the baseline levels before fentanyl (15,17). These hyperdynamic events are accompanied by elevations in circulating catecholamine levels (15) although the administration of naloxone by itself does not cause them to increase (18).

On the other hand, many clinical studies make no mention of circulatory problems after reversal with naloxone (19-23), and some have reported no differences in hemodynamics in awakening patients whether or not naloxone was given (24,25). Indeed, it appears that this agent has been used uneventfully

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and successfully in many thousands of patients since its introduction in 1970.

The cause of the occasional capricious effects of naloxone remains unknown. One of the variables to be considered is the arterial carbon dioxide tension existing before opioid reversal. If the patient is hypoventilating at this time, the abrupt restoration of the normal homeostatic responses to hypercapnia might be expected to precipitate not only a prompt increase in minute ventilation but also a marked adrenergic and associated hemodynamic response, as central control mechanisms are reestablished by the rapid injection of the opioid antagonist.

To determine the role of existing arterial carbon dioxide tension in events associated with narcotic reversal, we have examined the hemodynamic and adrenergic responses to acute narcotic reversal with naloxone during hypo-, normo-, and hypercapnia in a dog model (26). In addition, to ascertain to what extent autonomically mediated indirect excitatory cardiovascular effects might be "masked" or counteracted by the direct depressant effects of an elevated PCO_2 , an autonomically denervated animal preparation was exposed to reduced and to elevated carbon dioxide tensions.

Methods

These animal experiments were conducted within the guidelines of the American Physiological Society.

Three series of experiments were designed to investigate the effects of narcotic reversal with naloxone at three different levels of arterial carbon dioxide tension. These experiments were performed on the same six mongrel dogs (weight 15 ± 1 kg) in random order, so that each dog participated in each series and thus acted as its own control. Two weeks was allowed between experiments on any one dog. The fourth and final series of experiments, using the same six dogs, was designed to investigate the direct cardiovascular effects of carbon dioxide during complete autonomic block. In all experiments, the dogs were anesthetized with 10 mg/kg intravenous thiopental, paralyzed with 20 mg succinylcholine, and intubated. During controlled ventilation with 1.5% (inspired) enflurane in oxygen, tidal volume and rate were adjusted to achieve normal blood oxygen tensions with an arterial carbon dioxide tension of 35 mm Hg.

After induction of anesthesia, catheters were introduced percutaneously into a femoral artery for direct measurement of blood pressure and for blood sampling, and into a femoral vein for injection of drugs

and administration of intravenous fluids; 5% dextrose in lactated Ringer's solution at a rate of $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. ECG electrodes were attached, and heart rate and blood pressure (Statham transducer) were measured and recorded continuously (Hewlett-Packard series 7758B polygraph). Arterial blood samples were taken at the appropriate times for determination of blood gas tensions (Instrumentation Laboratories, model Micro 13) and for measurement of plasma levels of norepinephrine and epinephrine by high performance liquid chromatography (27). (Our laboratory inter- and intraassay variability for catecholamine determinations is $<6\%$, with a sensitivity of 10 and 20 pg/ml for norepinephrine and epinephrine, respectively [28].) Enflurane and carbon dioxide concentrations were measured continuously by mass spectrometry (Perkin-Elmer, model MGA 1100). Esophageal temperature was maintained at $38 \pm 0.5^\circ\text{C}$. All drugs used were commercial preparations: fentanyl citrate (Sublimaze, Janssen Pharmaceutica, NY); naloxone hydrochloride (Narcan, Du Pont Pharmaceuticals, Puerto Rico); succinylcholine chloride (Anectine, Burroughs-Wellcome, NC); tetracaine hydrochloride (Pontocaine, Breon Laboratories, NY); thiopental sodium (Pentothal, Abbott Laboratories, IL); and vecuronium bromide (Norcuron, Organon, NJ).

For the initial three series of experiments designed to assess the effect of hypo-, normo-, and hypercapnia on narcotic reversal, baseline measurements of heart rate, blood pressure, and plasma catecholamine levels were taken about 60 minutes after induction. Then fentanyl $50 \mu\text{g/kg}$, was infused over 5 minutes, and measurements were again taken 5 and 40 minutes thereafter. During the next 15 minutes, respiration was adjusted (using end-tidal carbon dioxide tension as a guideline) as required to produce the arterial carbon dioxide tension determined by the randomization protocol: 20 mm Hg (hypocapnic dogs) or 60 mm Hg (hypercapnic dogs). Ventilation in normocapnic dogs was not changed, so that their carbon dioxide tensions remained at 35 mm Hg. The nonparalyzed dogs were observed for signs of light anesthesia including respiratory movement; additional fentanyl was to have been given had this occurred, but none was required.

At the specified carbon dioxide tension, another set of measurements was taken. Preliminary experiments had indicated that hypercapnic dogs would fight the respirator after administration of naloxone, thus interfering with measurements. Therefore, all dogs were treated with vecuronium 0.1 mg/kg 2 minutes before naloxone 0.4 mg was given as a bolus. Measurements were taken 1, 5, and 10 minutes

thereafter; then normocapnia was restored. Enflurane was discontinued, and the percutaneous intravenous and arterial lines were removed. After adequate spontaneous respirations had returned, the dogs were extubated, observed until completely recovered, given naloxone 0.4 mg IM, and returned to the vivarium.

To assess the direct effects of varying carbon dioxide tensions on hemodynamic functions, a final series of experiments was performed after autonomic denervation in the same six dogs. Induction, intubation, and maintenance were the same as previously described, and ventilation was adjusted to obtain normocapnia (P_{aCO_2} 35 mm Hg). The femoral artery and vein were surgically isolated and cannulated, and the vagus nerves were isolated in the neck. A flow-directed pulmonary artery catheter was placed through the right external jugular vein. To prepare for subsequent spinal anesthesia, a 19-gauge catheter was surgically introduced into the subarachnoid space at the atlantooccipital junction and advanced to the lower lumbar level. Measurements consisted of those obtained in the previous three series of experiments plus continuous central venous and pulmonary arterial pressure and thermodilution cardiac outputs (Edwards computer, model 9520A) measured in duplicate.

After cardiovascular stability was obtained, dextrose in lactated Ringer's solution was given as needed to keep central venous and pulmonary capillary wedge pressures constant throughout the experiment. Baseline measurements were made, the vagi were severed in the neck, and then tetracaine was injected into the subarachnoid space in 5-mg increments at four equidistant points as the catheter was withdrawn along the thoracolumbar cord (total dose 20 mg). Measurements were taken when hemodynamic conditions were again stable. Fentanyl (50 μ g/kg) was infused over 5 minutes, and measurements were repeated 5 minutes later, still at normocapnia. Next, respiration was increased to reduce arterial carbon dioxide tension to 20 mm Hg, and repeat measurements were made. Finally, ventilation was decreased to produce an arterial carbon dioxide tension of 60 mm Hg, and measurements were repeated. Then 0.4 mg naloxone was given, and final measurements were done.

To summarize, the four series of experiments in each of the six dogs were as follows:

1. Fentanyl followed by reversal with naloxone during hypocapnia.
2. Fentanyl followed by reversal with naloxone during normocapnia.

3. Fentanyl followed by reversal with naloxone during hypercapnia.
4. Autonomic denervation, followed by fentanyl, normocapnia, hypocapnia, and hypercapnia in sequence, then reversal with naloxone.

Statistics

Before statistical analysis, plasma catecholamine levels were normalized through log conversion. Intraseries changes in these and in hemodynamic values were examined by means of analysis of variance for repeated measure, followed by Bonferroni's modified *t*-test. $P < 0.05$ was considered statistically significant. One-way analysis of variance was used to test for interseries differences. When significance was demonstrated ($P < 0.05$), individual differences (e.g., hypercapnic vs. normocapnic or hypocapnic dogs, etc.) were isolated using a weighted *t*-test in which the critical probability for significance (P) was calculated as P/g , where g was equal to the number of series of experiments in intact dogs. Thus, to achieve significance at the 5% level, P had to be $<0.05/3$ or <0.017 .

Results

All results are reported as mean values \pm SEM. Because the protocol for all experiments in the intact dogs was identical until the time of changing the arterial carbon dioxide tension, the data for the first three measurement points from the three series were pooled (Figs. 1-4). The rest of the measurement points are shown separately for each series and are compared only with their own paired values in the determination of intraseres changes.

Effect of CO₂ on Narcotic Reversal

The administration of fentanyl produced a significant and persistent decrease in heart rate (Fig. 1), mean arterial blood pressure (Fig. 2), and plasma norepinephrine (Fig. 4). Hemodynamic values remained unchanged during the next 45 minutes, but plasma levels of both catecholamines declined further (Figs. 3 and 4). Thus, epinephrine levels were also significantly below baseline values 45 minutes after fentanyl. Adjustment of the ventilation (as described in Methods) caused no significant intraseres changes in blood pressure or heart rate. However, even in the narcotized state, plasma levels of norepinephrine

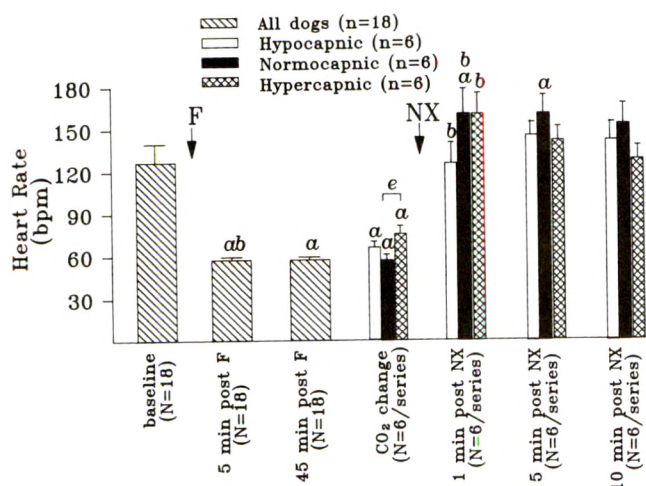


Figure 1. Mean (\pm SEM) heart rates in autotomically intact hypocapnic, normocapnic, and hypercapnic dogs at the time points indicated. Data from all experiments have been pooled for the three observations preceding change in CO_2 . Statistically significant differences ($P < 0.05$) are indicated as *a*, different from baseline values; *b*, different from preceding values; *c*, different from (paired) values before change in Paco_2 ; *d*, values in hypercapnic animals different from those in hypocapnic animals; *e*, values in hypercapnic animals different from those in normocapnic animals.

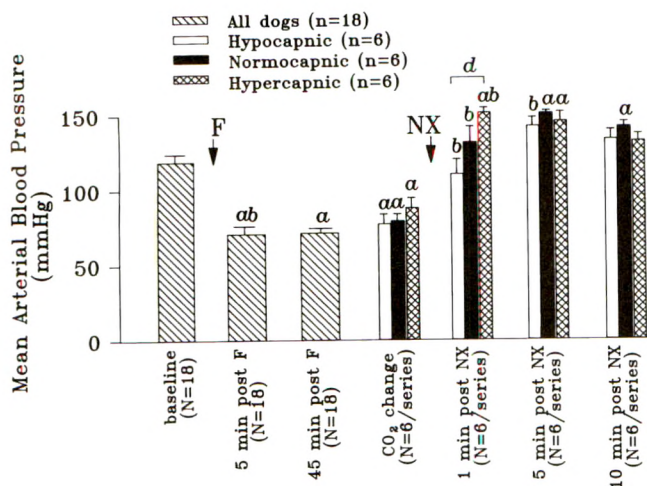


Figure 2. Mean values (\pm SEM) of mean arterial pressure in the three sets of experiments. See legend to Figure 1 for explanation.

(Fig. 4) increased when the dogs were made hypercapnic ($P < 0.01$), and at this time norepinephrine levels were significantly greater in hypercapnic than in either hypocapnic or normocapnic dogs ($P < 0.02$ for both). Although hypercapnia did not cause a significant increase in epinephrine levels, the absolute values reached were also significantly greater at this time than epinephrine levels in either hypocapnic ($P < 0.01$) or normocapnic ($P < 0.05$) dogs.

Naloxone caused a significant ($P < 0.001$) increase in heart rate over prenaloxone values in all three

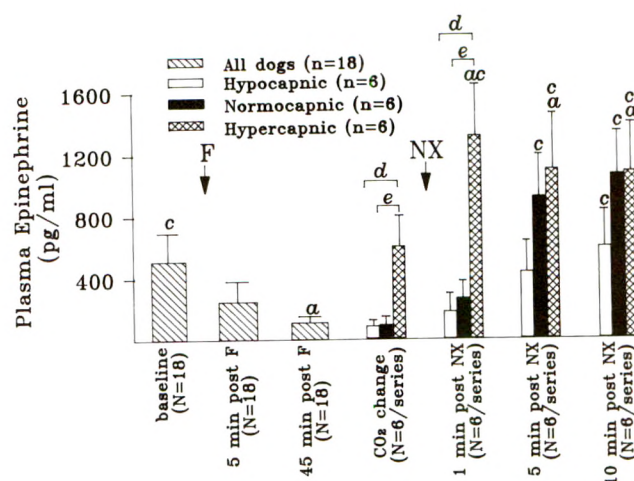


Figure 3. Plasma epinephrine levels (mean values \pm SEM). See legend to Figure 1 for explanation.

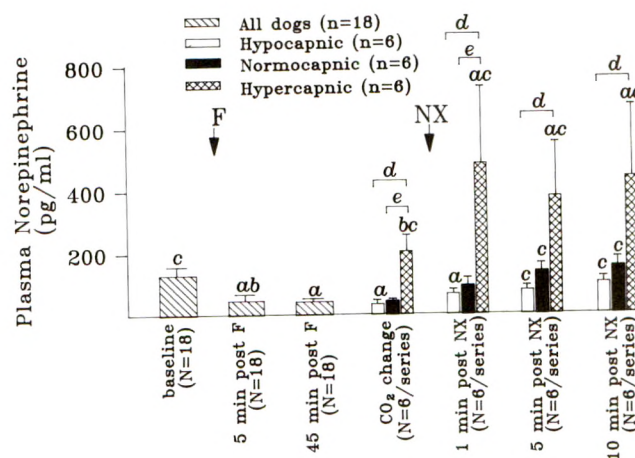


Figure 4. Plasma norepinephrine levels (mean values \pm SEM). See legend to Figure 1 for explanation.

groups 1, 5, and 10 minutes after its administration (Fig. 1). The heart rates were significantly greater than the prenaloxone baseline values only in normocapnic dogs, which had somewhat lower baseline heart rates on the days of those experiments; however, there were no interseries differences in the absolute heart rates at any time after naloxone. Mean blood pressure (Fig. 2) also increased significantly ($P < 0.003$) in all three groups 1 minute after naloxone, but the absolute values reached were significantly higher in hypercapnic dogs than in those with a low CO_2 ($P < 0.01$). Moreover, at this 1-minute time point, blood pressures were significantly greater than baseline levels only in hypercapnic dogs. By 5 and 10 minutes after naloxone, blood pressure had increased to greater than baseline values in normocapnic dogs also, but not in hypocapnic ones.

One minute after naloxone, plasma epinephrine levels were significantly higher in hypercapnic dogs

Table 1. Mean Values (\pm SEM) for Mean Arterial Blood Pressure (MABP), Heart Rate (HR), Cardiac Index (CI), and Systemic Vascular Resistance Index (SVRI) in Six Dogs Exposed to Normo-, Hypo-, and Hypercapnia, in Turn, after Parasympathetic and Sympathetic Block

	Baseline	After spinal	After fentanyl (35 mm Hg)	Hypocapnia (20 mm Hg)	Hypercapnia (65 mm Hg)	After naloxone
MABP (mm Hg)	107 \pm 8	82 \pm 9*,†	88 \pm 5	85 \pm 6	49 \pm 2*,†,‡	65 \pm 7*
HR (beats/min)	111 \pm 6	106 \pm 4	108 \pm 5	115 \pm 6	95 \pm 5*,†,‡	98 \pm 5*
CI (L min ⁻¹ ·m ⁻²)	4.4 \pm 0.4	4.0 \pm 0.4	4.0 \pm 0.3	4.7 \pm 0.4	4.3 \pm 0.3	4.5 \pm 0.4
SVRI (dynes·sec·cm ⁻⁵ ·m ²)	1993 \pm 178	1752 \pm 296	1848 \pm 210	1490 \pm 165	955 \pm 107*,‡	1178 \pm 127*

Statistically significant differences ($P < 0.05$) are indicated as * different from baseline; † different from preceding values; ‡ different from postfentanyl normocapnic values.

than in the other two series of experiments (Fig. 3). Moreover, only under hypercapnic conditions did the 1-minute epinephrine levels increase significantly over baseline values ($P < 0.01$), as well as over the levels present before the change in CO_2 ($P < 0.01$). Although there were later (5 and 10 minutes) increases in plasma epinephrine levels in the hypocapnic and normocapnic experiments also, these were never significantly increased over either prenaloxone or baseline values.

The administration of naloxone caused no significant increase in plasma norepinephrine levels in hypocapnic or normocapnic dogs (Fig. 4). Further elevation of norepinephrine (i.e., above the already elevated prenaloxone values) occurred in five of the six hypercapnic dogs, and at 1 minute after naloxone the mean norepinephrine level in the hypercapnic series was significantly greater than baseline. Individual increases in norepinephrine levels after naloxone ranged from 26 to 270%. The mean absolute norepinephrine level reached at 1 minute was also significantly greater than the mean value in either hypocapnic or normocapnic dogs ($P < 0.05$); these intergroup differences persisted throughout the 5- and 10-minute sampling periods.

Effect of CO_2 in the Absence of Autonomic Tone

After vagotomy and with the onset of spinal sympathetic blockade, there was a barely significant reduction in blood pressure ($P = 0.05$) and no change in heart rate, cardiac index, or systemic vascular resistance index (Table 1). Plasma epinephrine and norepinephrine decreased to scarcely detectable levels and remained so throughout the rest of the experiment, even when hypercapnia was instituted. In autonomically blocked dogs, the administration of neither 50 $\mu\text{g/kg}$ fentanyl nor 0.4 mg naloxone had any significant effect on any parameter measured.

Decreasing arterial carbon dioxide tension to 20 mm Hg had no hemodynamic effects (Table 1). How-

ever, hypercapnia caused persistent and significant decreases in heart rate, blood pressure, and systemic vascular resistance. Cardiac index was not affected by changes in arterial carbon dioxide tensions during autonomic blockade, nor were the very low levels of catecholamines.

Discussion

The influence of hypo- and hypercapnia on adrenergic and hemodynamic functions has been known for a long time. Hence it was obvious to explore the role of carbon dioxide tension on the magnitude of cardiovascular changes brought about by narcotic reversal. To elucidate the relative contributions of indirect, i.e., neurogenic and hormonal, and direct actions of Paco_2 on cardiovascular endorgans, the design included experiments in intact as well as in autonomically denervated animals.

Although the literature cites many examples of patients emerging from anesthesia in whom the administration of naloxone resulted in calamity (1-10), the arterial Pco_2 at the time of narcotic reversal is rarely stated. However, it would seem that patients emerging from anesthesia and being coaxed to breath spontaneously by a "light hand on the bag" are quite likely to have an elevated carbon dioxide tension, as will those patients who are hypoventilating in the recovery room. In our experiments in intact dogs, an attempt was made to mimic a nonhypoxic but hypercapnic patient awakening from inhalation anesthesia after a moderate dose of a narcotic, to whom a narcotic antagonist is given in a quantity sufficient to abruptly and completely reverse the residual narcosis.

In the 18 experiments carried out in our six autonomically intact dogs, the decreases in blood pressure and heart rate after administration of fentanyl were accompanied by reduced central sympathetic outflow, as reflected by significant decreases in plasma levels of catecholamines. The fact that the

alteration in autonomic tone was the only reason for the decreased hemodynamic function—that is, that the fentanyl had no direct actions on the endorgans—is confirmed by the lack of hemodynamic effect of fentanyl in the same dogs after pharmacologic autonomic denervation, as has been previously reported (29). Thus, one might say that in dogs under basal enflurane anesthesia and in the absence of stimulation, the fentanyl-induced relaxation of central sympathetic outflow approached, to some degree, that seen after sympathetic block.

Even after 50 $\mu\text{g/kg}$ of fentanyl, however, the rapid institution of fairly severe hypercapnia in the intact dogs significantly elevated sympathetic tone, as reflected in elevated plasma catecholamine levels, without significant changes in heart rate or blood pressure. This lack of accompanying excitatory changes in hemodynamic function may have been due to the concomitant and counteracting direct depressant effects of hypercapnia on the circulation (see later). In spite of the activation of central sympathetic outflow by hypercapnia alone, before naloxone, the intact dogs appeared still to be adequately anesthetized: none moved, and there were no respiratory efforts, without doubt because of the narcotic-induced shift of the CO_2 response curve.

The administration of naloxone to the intact dogs produced dramatic increases in cardiovascular and adrenergic functions even though the dogs remained under enflurane anesthesia. However, these changes occurred more rapidly and abruptly in hypercapnic dogs, so that absolute values of blood pressure, as well as plasma levels of both catecholamines, were highest in this series by 1 minute after naloxone and exceeded baseline values. In contrast, the responses of all measured variables occurred more slowly in both normocapnic and hypocapnic dogs and never exceeded baseline levels in the latter. Perhaps the rapid onset of the changes in circulatory and adrenergic functions brought about by naloxone reversal under hypercapnic conditions is as important in the etiology of the clinical problems described as are the absolute levels of blood pressure or plasma catecholamine concentrations reached.

Hypertension and tachycardia after naloxone were seen in dogs despite the fact that no attempt was made to replete the vascular volume as fentanyl decreased sympathetic tone. Some of the more profound hemodynamic events reported in the clinical literature, particularly those involving morphine, may have been exacerbated by an intraoperative relative volume overload (3). It is apparent from case reports of misadventure after naloxone administration that there is extreme variability in the sensitivity

of the cardiovascular center to narcotic antagonism in humans. Hypercapnia may account for some but not all of this variability. In all likelihood, the influence of existing arterial carbon dioxide tension (and pH) in clinical conditions is greater than that observed in the present experiments. To avoid pain and awareness, enflurane anesthesia was maintained in these dogs, and this inhalation anesthetic would have depressed the normal sensitivity to carbon dioxide. In human patients, however, inhalation anesthesia has usually been discontinued before administration of naloxone, and the resultant hemodynamic and adrenergic events can be expected to be even more marked in hypercapnic patients than those observed by us in these hypercapnic and anesthetized dogs.

Since each dog participated in all experiments, we had an opportunity to measure baseline plasma concentration levels under identical conditions four times. Although the induction of anesthesia was the same for all dogs, it was apparent that for any given dog baseline catecholamine values were extremely variable. Regardless of the baseline, fentanyl profoundly depressed plasma epinephrine and norepinephrine levels in all dogs. However, in one dog, catecholamine levels failed consistently to increase during narcotic reversal even though blood pressure and heart rate responses to naloxone administration were at or above the mean of the series at all carbon dioxide tensions. Clearly the hemodynamic response to narcotic reversal does not correlate in every case with plasma catecholamine levels as measured under our protocol.

As in dogs, baseline catecholamine levels will differ from patient to patient. The “more excitable” individual, with higher sympathetic tone, will experience a greater depression of cardiovascular and adrenergic function after narcotic administration (30,31). Therefore, it is not unreasonable to assume that such a patient will be stimulated to a greater than average extent by narcotic reversal, perhaps with a tendency to “overshoot,” resulting in the untoward hemodynamic events reported in the literature (1–10). Variability in abruptness and completeness of reversal may be additional factors.

The results after autonomic denervation indicate that when reflex sympathetic responses, with their resultant excitatory effect on the cardiovascular system, were eliminated, the direct circulatory effects of hypercapnia (negative chronotropic effect and systemic vasodilatation) were unmasked. These direct depressant effects of an elevated carbon dioxide tension, which have been reported also in dogs in whom reflex sympathetic activation was prevented by hexamethonium infusion (32), would tend to diminish the

magnitude of the indirect tachycardiac and pressor response. Perhaps this explains in part the fact that naloxone reversal brought about relatively greater differences in plasma catecholamines than in blood pressure between hypercapnic dogs and those in the other two series.

In conclusion, fentanyl is again shown to be without direct cardiovascular effects, although it is a potent depressor of central sympathetic outflow. However, even after fentanyl, inducing hypercapnia caused an adrenergic response in neurogenically intact dogs. Antagonism of the narcotic with naloxone further elevated plasma catecholamine levels and reversed the hemodynamic quiescence that fentanyl had induced. Reversal effects were more rapid in onset and greater in magnitude during hypercapnic conditions, in spite of the concomitant direct cardiovascular depressant effects of hypercapnia, as demonstrated after autonomic block.

These observations support the recommendation that normocapnia or slight hypocapnia should be established before naloxone is administered to the postanesthetic patient.

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The Roles of Acute and Chronic Pain in Regression of Sensory Analgesia During Continuous Epidural Bupivacaine Infusion

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MOGENSEN T, SCOTT NB, LUND C, BIGLER D, HJORTSØ N-C, KEHLET H. The roles of acute and chronic pain in regression of sensory analgesia during continuous epidural bupivacaine infusion. *Anesth Analg* 1988;67:737-40.

The purpose of this study was to investigate whether regression of sensory analgesia during constant epidural bupivacaine infusion was different in postoperative patients with acute pain than in patients with chronic nonsurgical pain. Sensory levels of analgesia (to pinprick) and pain (on a five-point scale) were assessed hourly for 16 hours during continuous epidural infusion of 0.5% plain bupivacaine (8 ml/hr) in 12 patients with chronic nonsurgical pain and in 30 patients after major abdominal surgery performed under combined bupivacaine and halothane—N₂O general anesthesia. No opiates were given. If sensory analgesia decreased more than five segments from the initial level or if

the pain score reached 2 (moderate pain), the patient was removed from the study. Initial levels of sensory analgesia after loading doses of 21.8 ± 0.5 and 19.3 ± 0.8 ml bupivacaine 0.5% were similar ($T_{3.8 \pm 0.3}$ and $T_{3.8 \pm 0.5}$) in the surgical and chronic pain patients, respectively (mean \pm SEM). Of the surgical patients, only 4 of the 30 (13%) maintained the initial level of sensory analgesia, and a pain score below 2 throughout the study compared with 7 of the 12 patients with chronic pain (58%) ($P < 0.01$). Mean duration of sensory blockade was significantly longer ($P < 0.005$) in the patients with chronic pain than in surgical patients (13.1 ± 1.2 and 8.5 ± 0.7 hours, respectively). Thus, surgical injury hastens regression of sensory analgesia during continuous epidural bupivacaine infusion. The underlying mechanism remains to be determined.

Key Words: PAIN, CHRONIC—postoperative. ANESTHETIC TECHNIQUES, EPIDURAL—bupivacaine.

Epidural blockade with local anesthetics in combination with light general anesthesia relieves pain during major abdominal surgery, but maintenance of the level of sensory analgesia and pain relief during the postoperative period is difficult as a result of both acute tolerance (tachyphylaxis) (1-5) and other factors (6,7). The semantics of "tachyphylaxis," which may be synonymous with acute tolerance rather than regression of sensory analgesia, are difficult, because the underlying mechanisms of these phenomena is unknown.

In previous studies, we demonstrated that the regression of analgesia during continuous postoperative infusion of epidural bupivacaine 0.5% 8 ml/hr is

independent of sex, weight, height, body surface area, serum albumin concentration, and the duration and site of surgery (8). Furthermore, administration of a double volume (16 ml/hr) of half-concentration (0.25%) bupivacaine could not prevent the decay of sensory analgesia (9). In contrast, pain alleviation with IV morphine (10) or epidural morphine (11) may reverse or prevent regression of sensory analgesia.

Experimental studies have demonstrated a hypersensitivity to pain after injury that is due to an increased excitability both peripherally and in the spinal cord (12,13). An explanation for the regression of analgesia during continuous postoperative epidural bupivacaine may, therefore, be a postoperative competitive increase in afferent input through the dorsal roots and spinal cord that overrides the initially effective neural blockade (14).

The purpose of this study was, therefore, to determine the speed of regression of sensory analgesia during continuous epidural bupivacaine infusion in patients with chronic pain (and assumed constant

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afferent input and stable peripheral and central nervous system excitability) and in patients with acute pain after abdominal surgery.

Methods

The study was approved by the Ethical Committee of the Municipality of Copenhagen, and informed consent was obtained from each patient.

Twelve patients scheduled for treatment with epidural morphine for severe chronic pain participated in the study. The diagnosis and the cause of the chronic pain was: bladder cancer ($n = 4$), stomach cancer ($n = 2$), primary hepatocellular cancer ($n = 1$), ovarian cancer ($n = 1$), metastatic pancreatic cancer ($n = 1$), metastatic breast carcinoma ($n = 1$), metastatic carcinoma from unknown primary site ($n = 1$), and senile osteoporosis with double vertebral crush fracture ($n = 1$). In 11 of the patients the pain was primarily from abdominal organs. The patient with vertebral crush fracture had pain from lumbar vertebrae. In these 12 patients an epidural catheter was inserted between L2 and L3 and bupivacaine 0.5% without epinephrine was used to produce a blockade from T4 to S5. After the bolus injection a pump-driven infusion of plain 0.5% bupivacaine at 8 ml/hr was initiated and scheduled to continue for 16 hours. The mean daily dose of opioid for pain treatment before initiation of the epidural bupivacaine infusion was 193 mg of morphine equivalents with a range from 30 to 900 mg. The patients had their normal dose of opioid the night before and were allowed to have additional opioid until 6 hours before the scheduled start of the treatment with epidural local anesthetics.

These 12 patients were compared with 30 patients scheduled for elective major abdominal surgery during combined epidural and general anesthesia with thiopental (3–5 mg/kg), precurarization with pancuronium (0.01 mg/kg), and succinylcholine (1.5 mg/kg) to facilitate orotracheal intubation. Anesthesia was maintained with N₂O/O₂ (2:1) and halothane (0.25–0.75%). The epidural catheter was inserted 30 minutes before anesthesia between L2 and L3, and plain bupivacaine 0.5% was used to produce a sensory blockade from T4 to S5 that was measured after 30 minutes. Immediately thereafter 0.5% plain bupivacaine was delivered by an infusion pump at a dose rate of 8 ml/hr and scheduled to continue for 16 hours after skin incision. Twenty-four of the 30 surgical patients have been described separately in a previous study (8). The patients in that study (8) and those in the present study were investigated within approximately the same period of time. The surgical proce-

dures included low anterior resections ($n = 7$), antrectomy ($n = 5$), right hemicolectomy ($n = 4$), upper abdominal explorative laparotomy ($n = 4$), small bowel resection ($n = 4$), pancreaticogastrostomy ($n = 2$), and cholecystectomy, rectal amputation, cystectomy, and sigmoid resection ($n = 1$ in each).

Pain scores on a five-point scale (no pain, slight pain, moderate pain, severe pain, unbearable pain) and level of sensory analgesia (to pinprick) were assessed hourly. If the level of sensory analgesia regressed more than five segments from the initial level or if the pain score reached 2 (moderate pain), the patient was removed from the study and pain was treated by other conventional methods.

Data were analyzed using Student's *t*-test for unpaired data and χ^2 -test (Yates-corrected); levels of $P < 0.05$ were considered statistically significant.

Results

The initial level of sensory analgesia was similar in the surgical group and in patients with chronic pain ($T_{3.8} \pm 0.3$ and $T_{3.8} \pm 0.5$, respectively) (mean \pm SEM, $p > 0.95$) after loading doses of bupivacaine 0.5% (21.8 ± 0.5 mL and 19.3 ± 0.8 mL, respectively [mean \pm SEM, $P < 0.05$]). The two groups were comparable with regard to clinical data (mean \pm SEM); height 168 ± 1 and 169 ± 1 cm; age 61 ± 3 and 67 ± 3 years; weight 63 ± 2 and 69 ± 4 kg; sex ratio (male/female) 13/17 and 7/5 in the surgical and chronic pain patients, respectively.

As seen in Figures 1 and 2, patients in both groups dropped out of the study with time because of a decrease in sensory analgesia of more than five segments below the initial level and/or increases in pain scores to 2 (moderate pain) or above. Thus, at 16 hours only 4 of the 30 patients in the surgical group (13%) remained in the study, in contrast to 7 of the 12 patients (58%) in the chronic pain group ($P < 0.01$) (Fig. 3). The mean duration of sensory analgesia was 8.5 ± 0.7 and 13.1 ± 1.2 hours, respectively ($P < 0.005$).

When one patient who received 900 mg of slow-release morphine sulfate per day was removed from the calculations, duration of analgesia was inversely correlated to daily consumption of morphine ($r = -0.69$, $P < 0.05$). No cardiovascular or respiratory complications were observed during the study.

Discussion

Acute tolerance, or "tachyphylaxis," is a well-known but poorly documented phenomenon in the postop-

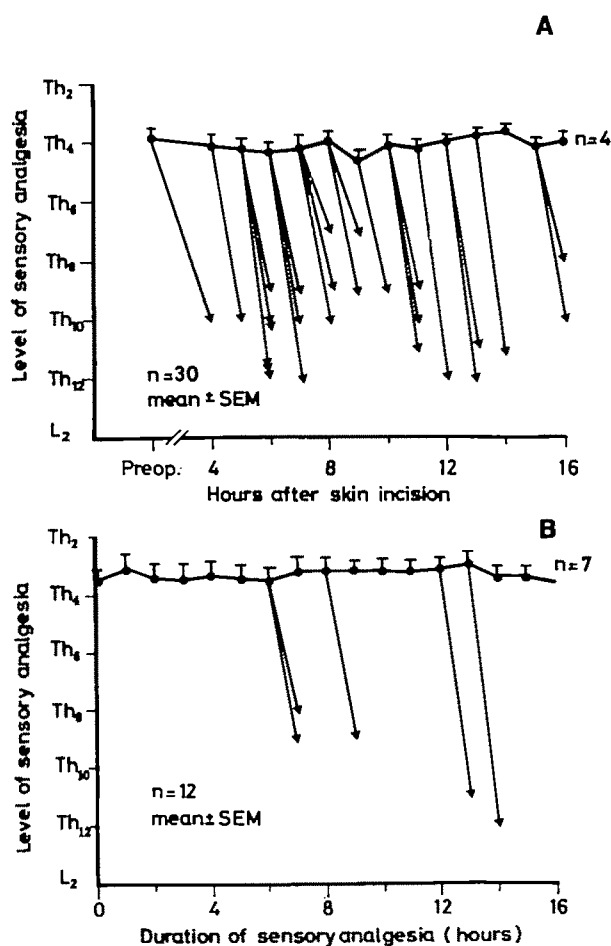


Figure 1. Decay of sensory level of analgesia during continuous epidural bupivacaine 0.5% 8 ml/hr (A) in patients who had abdominal surgery and (B) in patients with chronic nonsurgical abdominal pain.

erative period during continuous epidural infusion of local anesthetics. In all studies of continuous infusion regimens (2-5), it was necessary to change the infusion regimen to maintain acceptable analgesia, and no data are available from infusion regimens with a constant dose rate in the study period.

In this study of 30 postoperative patients, only 4 patients maintained a stable level of sensory analgesia and low pain score during a constant infusion rate of bupivacaine 0.5% (8 mL/hr) for 16 hours.

The explanation for regression of sensory analgesia and/or tachyphylaxis remains unknown (7), but several hypotheses exist, including a decreased effect on receptors because of increased cyclic-AMP (15), decrease in pH (16), increase in sodium concentration in the epidural space (7), or decreased amount of drug available at the receptors due to increased absorption or altered distribution in the epidural space. In light of recent information on the physiology of the nociceptive systems, we have proposed an

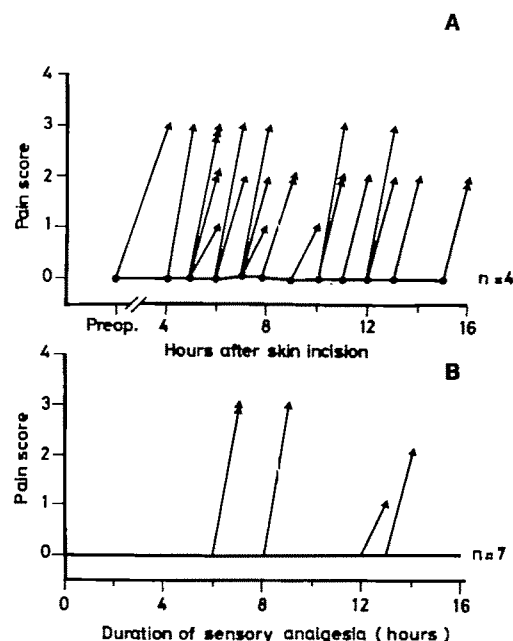


Figure 2. Increase in pain scores during continuous epidural bupivacaine 0.5% 8 ml/hr (A) in patients after abdominal surgery and (B) in patients with chronic nonsurgical abdominal pain.

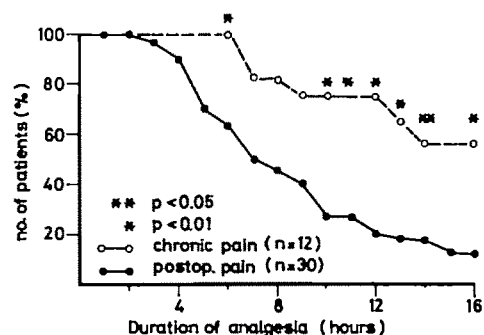


Figure 3. Percentage of postoperative and chronic pain patients who maintained initial level of sensory analgesia during epidural bupivacaine 0.5% 8 ml/hr.

additional mechanism (14). Experimental studies have demonstrated that there is an increase in peripheral afferent input or an increased excitability in peripheral nociceptors and the spinal cord after peripheral trauma (12,13). If similar changes in afferent neural transmission occur in the postoperative period, the blocking effect of epidural bupivacaine may be overridden, thereby reducing sensory analgesia in the rostral part of the neural blockade where the intensity of the blockade and the concentration of bupivacaine are presumably at their lowest. In previous studies we found that both systemic and epidural morphine can counteract the regression in sensory analgesia in postoperative patients (10,11). The explanation is unknown, but the effect may be due to activation of so-called off-cells in the rostral ventral

medulla which then activate descending inhibitory pain-modulating circuits as shown in experimental models (17). These changes may then lead to a reduction in postoperative spinal excitability, thereby supporting the maintenance of neural blockade and initial level of sensory analgesia.

In this study the patients with chronic nonsurgical pain had severe pain caused by cancer or osteoporosis despite treatment with high doses of opioids. A high level of afferent input from the periphery or an increased excitability in the spinal cord may be an important factor in determining the duration of sensory analgesia because of the demonstrated inverse correlation between duration of sensory analgesia and the daily dose of morphine needed to treat pain. Patients who received the lowest dose of morphine, presumably because of the lowest degree of pain, also had a more stable and prolonged duration of sensory analgesia. The only exception to this was a patient treated with a very high dose of slow-release morphine (900 mg daily) who maintained pinprick analgesia for 16 hours. This could be due to a relatively high concentration of morphine in the CNS in the 22 hours after the last administration of morphine, since our other studies have shown that morphine prevents regression of analgesia in postoperative patients (10,11). Although we cannot rule out that the morphine the patients with chronic pain received had a positive influence and thereby prevented acute tolerance, we do not think that this is an important factor, because the patient who received the largest dose had the quickest development of acute tolerance.

It could be argued that some decay in sensory level of analgesia may be expected after epidural injection of a large volume of local anesthetic solution in the lumbar region followed by a rather low volume infusion rate. However, this does not explain the great interindividual difference in rate of regression of analgesia in both groups of patients or the difference between surgical and nonsurgical patients in duration of sensory analgesia. Furthermore, a double-volume, half-concentration infusion regimen did not prevent regression of sensory analgesia postoperatively (9). An alternative explanation is that the decay in sensory analgesia is the result of an increased absorption of bupivacaine due to a postoperative increased blood flow in the epidural space, but no data are available to support this hypothesis.

In conclusion, our results show that patients with chronic pain have a more stable level of sensory analgesia during continuous epidural bupivacaine infusion than do postoperative patients. The explanation for this is unknown, but postoperative hyper-

sensitivity in the spinal cord, a higher afferent neural input, or increased elimination of bupivacaine from the epidural space may be contributing mechanisms.

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Prolongation of the QT Interval by Volatile Anesthetics in Chronically Instrumented Dogs

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RILEY DC, SCHMELING WT, AL-WATHIQUI MH, KAMPINE JP, WARLTIER DC. Prolongation of the QT interval by volatile anesthetics in chronically instrumented dogs. *Anesth Analg* 1988;67:741-9.

The influence of volatile anesthetics on ventricular repolarization in vivo (QT interval) has not been studied in a systematic fashion. The purpose of this investigation was to characterize the electrocardiographic and hemodynamic actions of the volatile anesthetics halothane, isoflurane, and enflurane in chronically instrumented dogs. Because autonomic nervous system tone may influence ECG findings, experiments were completed with and without concomitant pharmacologic autonomic nervous system blockade. In six groups comprising 50 experiments with 21 instrumented dogs, anesthesia was mask-induced with nitrous oxide, oxygen, and one of the volatile anesthetics and maintained with the volatile anesthetic in 100% oxygen for 2 hours. Changes in the ECG and in hemodynamics were compared to the conscious state. In the absence of autonomic nervous system blockade, halothane and isoflurane significantly

prolonged the QT interval (0.24 ± 0.01 to 0.30 ± 0.01 second and 0.22 ± 0.01 to 0.28 ± 0.01 second, respectively), whereas enflurane produced no change in ventricular repolarization (0.24 ± 0.01 to 0.26 ± 0.01 second). All of the volatile anesthetics increased the QT interval corrected for changes in basal heart rate (QT_c), and all agents decreased intravascular pressure and dP/dt . Following autonomic nervous system blockade, halothane, isoflurane, and enflurane significantly increased the QT interval and QT_c . The results demonstrate that ventricular repolarization is directly altered by the volatile anesthetics independent of changes in autonomic nervous tone. Whether or not such effects are additive with other congenital or acquired forms of QT_c prolongation has yet to be examined. The present results indicate that caution should be used during the administration of volatile anesthetics to patients with abnormalities of the QT interval.

Key Words: ANESTHETICS, VOLATILE—enflurane, halothane, isoflurane. HEART, ELECTROCARDIOLOGY—QT interval.

The QT interval measured from the beginning of the QRS complex to the end of the T wave represents the total duration of ventricular systole, including myocardial depolarization and repolarization (1). This interval is rate-dependent and must be corrected for changes in basal heart rate for comparison (the corrected QT expressed as the QT_c). Prolongation of the QT_c has been shown to increase the period of vulnerability of the heart to arrhythmias (relative refractory

period) as well as to increase the incidence of ventricular premature beats. Both of these phenomena have been demonstrated to lead to development of reentrant arrhythmias such as ventricular fibrillation, leading to syncope or sudden cardiac death (2-8).

Prolongation of the QT_c may exist in congenital (primary) or acquired (secondary) forms. The congenital forms of prolongation of the QT interval include an autosomal recessive syndrome associated with congenital neural deafness (9-13) and a more frequently occurring autosomal dominant syndrome with no hearing loss (13-17). The causes of acquired prolonged QT_c are many: they include cardiac and nervous system disturbances; thermal, electrolyte, endocrine, and metabolic disturbances; and pharmacologic agents (18).

Although direct effects of thiopental and succinylcholine prolong the QT_c in humans (19), the direct

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effects of the volatile anesthetics have not been systematically examined. Previous studies indicate that halothane and enflurane in children (20) and isoflurane in the dog (21) may prolong the QT interval, but the concomitant presence of other agents has complicated interpretation of the results. Thus the direct effects of halothane, isoflurane, and enflurane on the QT interval have yet to be examined (18).

The present investigation was designed to evaluate the direct electrocardiographic and hemodynamic effects of halothane, isoflurane, and enflurane in the chronically instrumented dog. Because the autonomic nervous system may play an important role in prolongation of the QT interval, anesthesia was administered with and without concomitant autonomic nervous system blockade.

Methods

Experimental Preparation

Approval for animal use in this study was granted by the Animal Care Committee of the Medical College of Wisconsin. Conditioned mongrel dogs of either sex weighing between 20 and 30 kg fasted overnight, and anesthesia was induced with sodium thiamylal (10 mg/kg IV). After tracheal intubation with a cuffed endotracheal tube, anesthesia was maintained with halothane (1.0–1.5%) in 100% oxygen (2 L/min) via a respirator (Monaghan 300 D/M; 9–12 breaths/min; tidal volume of 15 ml/kg). Atelectasis was prevented by maintaining an end expiratory pressure at 5 cm H₂O. The left lateral chest wall was shaved, scrubbed, disinfected, and draped. Under sterile conditions, a thoracotomy was performed in the left fifth intercostal space and the lungs gently retracted. Heparin-filled catheters were directly inserted and secured in position in the thoracic aorta and right atrial appendage for measurement of aortic blood pressure (Statham P50) and drug administration, respectively. The position of all catheters was confirmed during surgery by palpation and on completion of the experiment after killing each dog.

The heart was suspended in a pericardial cradle and a 1.5–2.0-cm section of the proximal left anterior descending (distal to the first diagonal branch) was carefully isolated. A precalibrated Doppler ultrasonic flow transducer (20 MHz) was placed on the vessel for measurement of phasic and mean coronary blood flow velocity. A catheter was positioned in the left atrial appendage. A high-fidelity miniature micromanometer (Koningsberg, P7) was inserted in the left ventricle through a stab wound in the apex and tightly secured for recording of left ventricular pres-

sure. The intraventricular transducer was cross-calibrated via measurements of systolic arterial and diastolic left atrial pressures from fluid-filled catheters. The maximum rate of rise of left ventricular pressure (peak positive dP/dt), an index of global left ventricular contractility, was measured by electronic differentiation of the ventricular pressure waveform. A triangular wave signal with known slope was used to calibrate the differentiator. Electrocardiographic leads (corresponding to limb lead II) were sutured to the internal thoracic wall. The chest was closed in layers, and the pneumothorax was evacuated by a chest tube with suction drainage. Each dog was fitted with a jacket to prevent damage to the instruments and catheters, which were housed in an aluminum box within the jacket pocket. After surgery, each dog recovered for 7–10 days before experimentation and was treated with 400,000 U procaine penicillin G and 560 mg dihydrostreptomycin, IM. During the postoperative recovery period, the dogs were trained to stand quietly in a sling during hemodynamic monitoring.

The ECG and all other hemodynamic parameters were recorded continuously on a polygraph (Hewlett-Packard). In addition, arterial blood samples were obtained at various intervals for measurement of blood gas tensions (ABL 2). Hemodynamics were digitized by means of an analog-to-digital converter (ISAAC 91A) interfaced to an Apple IIe computer (22). The average values of eight consecutive cardiac cycles were utilized. Hemodynamic variables were calculated for each cardiac cycle and reported as the average over the completed cycles in the collection. Because conscious dogs have a prominent sinus arrhythmia, data were collected during periods of expiration at a stable hemodynamic state. The PR interval, QRS duration, RR interval, and QT interval were determined directly from ECG stripchart recordings. The average values of five independent determinations of ECG variables from different cardiac cycles were used. The QT interval was corrected for the level of heart rate (QT_c) by dividing the QT interval by the square root of the RR interval (23).

Experimental Protocol

Six groups of experiments with a total of 21 instrumented dogs were performed during which hemodynamics and the ECG were continuously recorded. All dogs fasted overnight, and before experimentation fluid deficits were corrected with crystalloid (0.9% normal saline) and maintenance continued with 3 ml · kg⁻¹ · hr⁻¹ for the duration of each experiment.

In three separate groups, the electrocardiographic and hemodynamic effects of halothane ($n = 10$), isoflurane ($n = 11$), and enflurane ($n = 10$) anesthesia were studied. After a 30-minute control period in the conscious state, anesthesia was mask-induced (with one of the volatile agents, 67% nitrous oxide, and 33% oxygen, at total flow rates of 8–10 L/min). The trachea was then intubated with a cuffed endotracheal tube, positive pressure ventilation initiated, and anesthesia maintained for 2 hours at inspired concentrations of either 2% halothane, 2% isoflurane, or 4% enflurane in 100% oxygen (2 L/min). The concentration of each anesthetic was selected to provide a 20–30 mm Hg decrease in mean arterial pressure. Halothane, isoflurane, and enflurane were each delivered into the gas flow by means of Fluotec MK3, Ohio Fortec, and Ohio Ethrane vaporizers, respectively. A gas mass spectrometer (model MGA-1100, Perkin-Elmer, Pomona, CA) was used to calibrate the vaporizers. Blood anesthetic concentrations of the anesthetics were measured 2 hours after intubation by gas chromatography with flame ionization detection (24). Millimolar concentrations in arterial blood correspond closely to end-tidal concentrations of volatile anesthetics.

In an additional three groups of experiments, electrocardiographic and hemodynamic effects of halothane ($n = 6$), isoflurane ($n = 6$), and enflurane ($n = 7$) were determined as described earlier in dogs with autonomic nervous system blockade. After a 30-minute conscious control period, propranolol (2.0 mg/kg), atropine (3.0 mg/kg), hexamethonium (20.0 mg/kg), and phentolamine (2.0 mg/kg; supplemented by 0.25 mg·kg⁻¹·hr⁻¹) were administered IV, and hemodynamics and electrocardiographic data again recorded. Adequacy of blockade was confirmed by absence of hemodynamic response to IV epinephrine and acetylcholine and lack of reflex changes in heart rate after administration of vasopressin. Previous studies from this laboratory have also indicated the doses of the above agents to be sufficient to produce autonomic nervous system blockade for the time course of the experiment (25). After pharmacologic blockade of the autonomic nervous system, 1.5–2% halothane, 1.75–2% isoflurane, or 3–4% enflurane (inspired concentrations) were administered in oxygen 2 L/min for 2 hours as described earlier. Slightly lower inspired concentrations of anesthetics were used in some experiments after autonomic blockade so as to avoid hemodynamic failure; however, arterial blood anesthetic concentrations in experiments with and without autonomic blockade were in close agreement. The ECG and all hemodynamics were again monitored.

Statistical Analysis

Data during control, autonomic nervous system blockade, and anesthetic intervention were compared by means of analysis of variance (26) followed by Dunnett's modification of the *t*-test. Differences between conscious state and anesthesia were considered statistically significant when the probability (*P*) value was <0.05. All data are expressed as mean ± SEM.

Results

Hemodynamic and Electrocardiographic Effects of Volatile Anesthetics

Halothane anesthesia (2% inspired corresponding to blood levels of 1.75 ± 0.13 mM) significantly ($P < 0.05$) reduced aortic pressure, left ventricular systolic pressure, and peak positive dP/dt, whereas no significant change was observed in heart rate as compared to the conscious state (Table 1). A small (insignificant) decrease in mean coronary blood flow velocity was observed. In contrast, isoflurane (2% inspired corresponding to blood levels of 1.78 ± 0.10 mM) significantly increased heart rate and decreased arterial pressure and left ventricular systolic pressure (Table 2). Whereas isoflurane produced a decrease in dP/dt smaller than that seen with halothane, isoflurane tended to increase coronary flow velocity. Enflurane (4% inspired concentration corresponding to blood levels of 4.14 ± 0.35 mM) also significantly increased heart rate concomitant with decreases in aortic pressure, left ventricular systolic pressure, and peak positive dP/dt (Table 3). No changes in left ventricular end diastolic pressure or coronary blood flow velocity were observed. No alteration in arterial pH and Pco₂ were observed during maintenance of volatile anesthesia; Po₂, however, significantly increased secondary to ventilation with 100% oxygen.

Halothane and isoflurane prolonged both the QT interval and the QT interval corrected for changes in heart rate (QT_c) (Figs. 1 and 2). In contrast, enflurane had a relatively smaller effect on the QT interval; however, when corrected for the basal change in heart rate (QT_c), significant prolongation of repolarization was observed (Fig. 3). Isoflurane and enflurane produced no change in the PR interval or QRS duration, whereas halothane was found to significantly increase the PR interval.

Hemodynamic and Electrocardiographic Effects of Volatile Anesthetics in the Presence of Autonomic Nervous System Blockade

Autonomic nervous system blockade with proprano-

Table 1. Summarized Hemodynamic and Blood Gas Data Before and After Halothane in Dogs With and Without Autonomic Nervous System (ANS) Blockade

	No ANS Blockade (n = 10)		After ANS Blockade (n = 6)	
	Conscious	Halothane	Conscious	Halothane
Heart rate (beats/min)	84 ± 5	87 ± 5	108 ± 9	74 ± 8*
Mean arterial pressure (mm Hg)	105 ± 5	85 ± 5*	65 ± 6	54 ± 6
Left ventricular systolic pressure (mm Hg)	124 ± 5	90 ± 6*	90 ± 6	68 ± 6*
Left ventricular end diastolic pressure (mm Hg)	10 ± 1	12 ± 1	11 ± 2	8 ± 1
+dP/dt (mm Hg/sec)	2650 ± 220	1120 ± 160*	1300 ± 180	730 ± 120*
Mean coronary blood flow velocity (Hz × 10 ²)	32 ± 4	23 ± 4	21 ± 2	15 ± 1*
pH (units)	7.40 ± 0.01	7.40 ± 0.02	7.37 ± 0.01	7.38 ± 0.02
Pao ₂ (mm Hg)	97 ± 4	535 ± 44*	93 ± 4	553 ± 15*
Paco ₂ (mm Hg)	32.4 ± 0.8	30.9 ± 1.1	33.5 ± 1.0	32.5 ± 2.1

Mean ± SEM data.

*Significantly ($P < 0.05$) different from respective conscious state.**Table 2.** Summarized Hemodynamic and Blood Gas Data Before and After Isoflurane in Dogs With and Without Autonomic Nervous System (ANS) Blockade

	No ANS Blockade (n = 11)		After ANS Blockade (n = 6)	
	Conscious	Isoflurane	Conscious	Isoflurane
Heart rate (beats/min)	88 ± 5	118 ± 5*	105 ± 8	73 ± 5*
Mean arterial pressure (mm Hg)	103 ± 3	83 ± 3*	60 ± 6	50 ± 4
Left ventricular systolic pressure (mm Hg)	126 ± 4	95 ± 3*	88 ± 7	71 ± 3*
Left ventricular end diastolic pressure (mm Hg)	10 ± 1	9 ± 1	9 ± 2	7 ± 3
+dP/dt (mm Hg/sec)	2800 ± 220	1580 ± 140*	1440 ± 190	960 ± 100*
Mean coronary blood flow velocity (Hz × 10 ²)	30 ± 4	41 ± 7*	27 ± 4	27 ± 5
pH (units)	7.40 ± 0.01	7.35 ± 0.02	7.37 ± 0.01	7.35 ± 0.02
Pao ₂ (mm Hg)	90 ± 6	577 ± 35*	92 ± 2	582 ± 37*
Paco ₂ (mm Hg)	33.7 ± 1.1	34.2 ± 1.5	34.4 ± 0.1	34.3 ± 1.4

Mean ± SEM data.

*Significantly ($P < 0.05$) different from respective conscious state.

lol, atropine, phentolamine, and hexamethonium resulted in a significant increase in heart rate (91 ± 3 to 104 ± 4 beats/min), and significant decreases in mean aortic pressure (100 ± 3 to 66 ± 4 mm Hg) and left ventricular systolic pressure (127 ± 4 to 90 ± 4 mm Hg) and peak positive dP/dt (2700 ± 140 to 1340 ± 90 mm Hg/sec). No changes in PR interval and QRS duration were observed, but the QT interval and QT_c increased significantly from 0.22 ± 0.01 to 0.27 ± 0.01 second and from 0.28 ± 0.01 to 0.36 ± 0.01 second, respectively. No effect of autonomic nervous system blockade on arterial blood gas tension was observed.

After autonomic nervous system blockade, the volatile anesthetics also decreased intravascular pressure (Tables 1-3). Furthermore halothane, isoflurane,

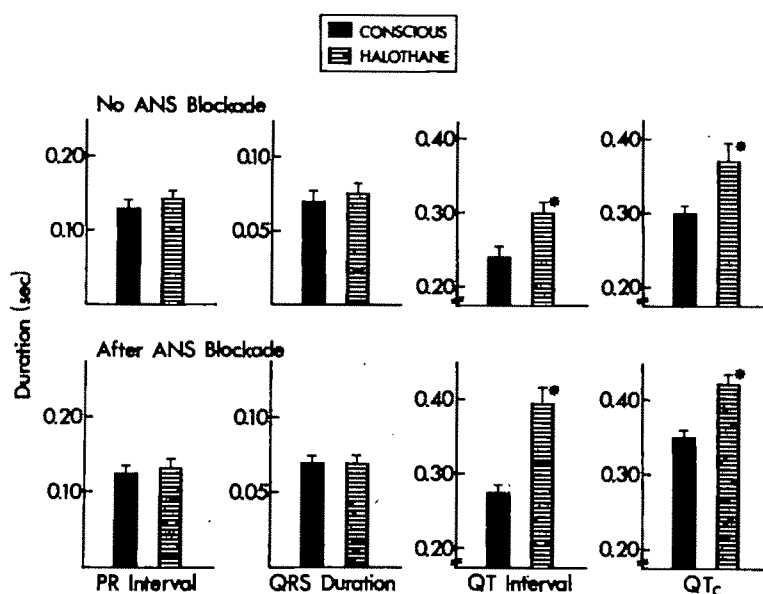
and enflurane in arterial concentrations of 1.97 ± 0.13 , 1.71 ± 0.27 , and 4.44 ± 0.62 mM, respectively, significantly decreased heart rate and peak positive dP/dt. No changes in left ventricular end diastolic pressure or mean coronary blood flow velocity were observed. In all groups, ventilation with 100% oxygen significantly increased Pao₂ without change in Paco₂ or pH.

In the presence of autonomic nervous system blockade, halothane, isoflurane, and enflurane increased both the QT interval and QT_c. Typical ECG stripchart recordings before and after autonomic nervous system blockade and after isoflurane anesthesia are shown in Figure 4. No change was observed in PR interval or QRS duration. Two dogs developed ventricular ectopy including ventricular tachycardia and

Table 3. Summarized Hemodynamic and Blood Gas Data Before and After Enflurane in Dogs With and Without Autonomic Nervous System (ANS) Blockade

	No ANS Blockade (n = 10)		After ANS Blockade (n = 7)	
	Conscious	Enflurane	Conscious	Enflurane
Heart rate (beats/min)	82 ± 4	108 ± 4*	101 ± 5	68 ± 4*
Mean arterial pressure (mm Hg)	102 ± 4	71 ± 5*	71 ± 9	49 ± 5*
Left ventricular systolic pressure (mm Hg)	121 ± 4	86 ± 4*	91 ± 8	57 ± 5*
Left ventricular end diastolic pressure (mm Hg)	10 ± 1	9 ± 1	7 ± 2	4 ± 2
+dP/dt (mm Hg/sec)	2670 ± 180	930 ± 70*	1300 ± 140	650 ± 100*
Mean coronary blood flow velocity (Hz × 10 ²)	28 ± 3	25 ± 3	27 ± 3	17 ± 4*
pH (units)	7.39 ± 0.01	7.38 ± 0.02	7.34 ± 0.02	7.36 ± 0.02
Pao ₂ (mm Hg)	89 ± 3	462 ± 22*	95 ± 3	548 ± 17*
Paco ₂ (mm Hg)	32.5 ± 1.1	32.8 ± 1.6	33.5 ± 1.0	32.5 ± 2.1

Mean ± SEM data.

*Significantly ($P < 0.05$) different from respective conscious state.**Figure 1.** Changes in length of PR interval, QRS duration, QT interval, and QT_c produced by halothane without and with autonomic nervous system blockade. Mean ± SEM data. *Significantly ($P < 0.05$) different from the conscious state.

fibrillation in the present study. Both dogs were anesthetized with enflurane after autonomic nervous system blockade.

Discussion

The purpose of this study was to evaluate the direct electrocardiographic and hemodynamic effects of the volatile anesthetics halothane, isoflurane, and enflurane in chronically instrumented dogs. Because changes in autonomic nervous system tone may be associated with changes in the QT interval, anesthetic actions were studied with and without pharmacologic blockade of the autonomic nervous system. The results demonstrated that halothane and isoflurane

each prolonged the QT interval in the presence and absence of autonomic blockade. Although enflurane produced no significant effect on the QT interval (a significant increase was observed only in QT_c) in the absence of autonomic nervous system blockade, this interval was markedly prolonged in the presence of autonomic blockade. Enflurane anesthesia during autonomic blockade extended QT_c to values greater than 0.44 second, a value considered to be the upper limit of normal in humans. Coincidentally, the only two dogs in the present experiments that developed ventricular ectopy (ultimately leading to ventricular tachycardia and fibrillation) were anesthetized with enflurane during autonomic nervous system blockade. A shortcoming of the present investigation was

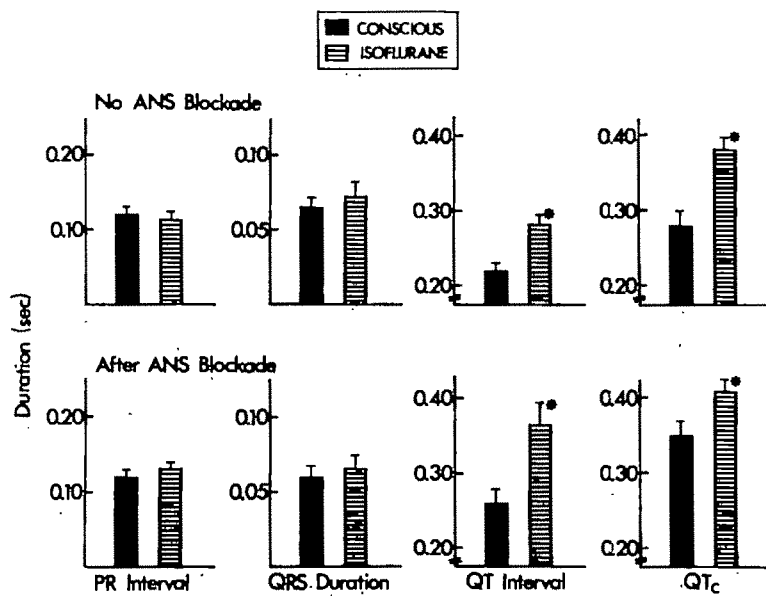


Figure 2. Changes in length of PR interval, QRS duration, QT interval, and QT_c produced by isoflurane without and with autonomic nervous system blockade. Mean \pm SEM data. *Significantly ($P < 0.05$) different from the conscious state.

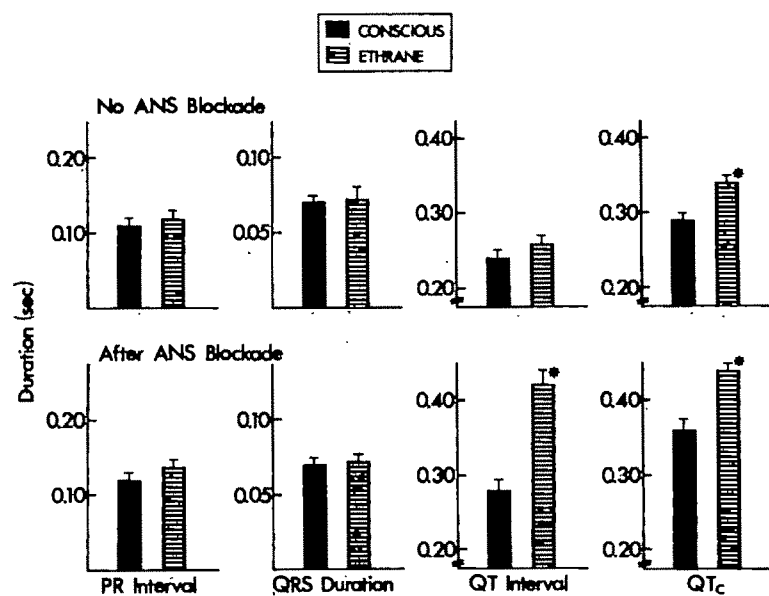


Figure 3. Changes in length of PR interval, QRS duration, QT interval, and QT_c produced by enflurane (Enflurane) without and with autonomic nervous system blockade. Mean \pm SEM data. *Significantly ($P < 0.05$) different from the conscious state.

that dose-response relations for the effect of each anesthetic on QT interval were not characterized. Only single concentrations of anesthetics were selected.

Whereas halothane had no effect and isoflurane and enflurane increased heart rate without autonomic nervous system blockade, all agents produced a decrease in heart rate with autonomic blockade. These results are consistent with previous *in vitro* studies showing direct negative chronotropic effects in isolated guinea pig sinoatrial node cells with halothane, isoflurane, and enflurane (27). Although halothane, isoflurane, and enflurane decreased peak positive dP/dt , an index of global contractility (with and without autonomic blockade), isoflurane was least

depressant. Consistent with these findings, previous studies have shown that isoflurane produces less of a negative inotropic effect than do halothane or enflurane (28-31).

That the QRS interval was unchanged by volatile anesthesia in the present investigation indicates that prolongation of QT_c reflected delayed repolarization. The use of the QT interval as a reflection of repolarization requires the end of the T wave to correspond to the longest duration of ventricular repolarization (5). A "silent repolarization" period resulting from canceled potential differences may exist at the end of the T wave, causing the QT interval to be a less sensitive indicator of repolarization changes (32). However, experiments in dogs (33) and humans (34)

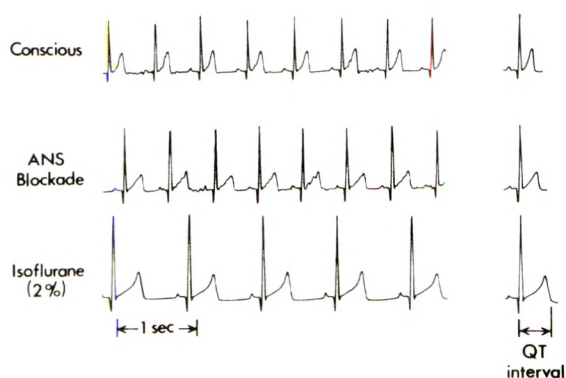


Figure 4. Typical stripchart electrocardiographic recording from a chronically instrumented dog before and after pharmacologic autonomic nervous system (ANS) blockade and after isoflurane (2% inspired concentration). Note marked prolongation of the QT interval without change in PR interval and QRS duration.

have demonstrated cardiac action potential termination before the end of the T wave.

Because prolonged QT_c may represent imbalanced cardiac sympathetic activity (32,35-38), pharmacologic blockade of sympathetic and parasympathetic influences was used in this investigation to observe the direct effects of halothane, isoflurane, and enflurane on QT_c . Each of the volatile anesthetics significantly prolonged QT_c in the absence of alterations in autonomic nervous system activity.

In healthy children with normal serum electrolytes, Lindgren (20) found that enflurane prolonged the QT_c whereas halothane produced no change or shortened the QT_c , the latter in contrast with results of the present study. Kentala and Saarnivaara, in agreement with the present investigation, observed in normal adults that halothane (0.5-2.0%) prolonged QT_c . These investigators, however, utilized other agents during induction, thus confounding the results (19,39,40). For example, when used during induction, thiopental, which has been shown to produce QT_c prolongation (19), makes results difficult to interpret for subsequent maintenance anesthesia with halothane or isoflurane. The residual effects of the barbiturate may be present during volatile anesthesia. In preliminary studies in the dog, isoflurane has been found to prolong the QT_c , but barbiturates were also used in these studies (21). Barbiturates were eliminated from the present study by using mask induction with nitrous oxide, oxygen, and one of the volatile anesthetics and maintaining anesthesia for 2 hours with the volatile anesthetic in 100% oxygen.

Although the mechanism of the delay in repolarization produced by halothane, isoflurane, or enflurane in this study is unknown, it is possible that the volatile anesthetics examined affect ion transport

in myocyte membranes. Lynch (41) found that 1-4% isoflurane increased the duration of action potentials in guinea pig papillary muscle by 7-11%. However, in a previous study, Lynch et al. (42) reported a dose-dependent decrease in the action potential duration of in vitro guinea pig papillary muscle by up to 24% of control at a concentration of 3.0% halothane. These results are consistent with a halothane-induced decrease in Ca^{2+} influx via slow channels. It has also been reported that halothane reduced duration of the action potential and shortened the effective refractory period in sheep ventricular cells (43). Similarly, enflurane at 3.0% and greater concentrations has been demonstrated to decrease action potential duration and diminish the plateau phase of guinea pig ventricular muscle (44). This change was also attributed to a decrease in the slow calcium channel-mediated current.

Reynolds et al. (45) have documented a decrease in the terminal repolarization of canine Purkinje fibers during administration of 2% halothane. However, coupled with this prolongation was an increase in the slope with a decreased duration of the plateau phase (phase 2 repolarization) resulting in little change in total action potential duration. Turner et al. (46) have recently documented a decrease in the action potential duration in normal Purkinje fibers by administration of halothane in vitro. In contrast, halothane prolonged the action potential duration of fibers from regions previously infarcted. Turner et al. (46) speculated that an inhibition of the slow inward calcium current with subsequent alteration in outward potassium current and delayed repolarization might be related to the halothane-induced increase in action potential duration observed in the infarcted tissue.

It is difficult to reconcile the above in vitro results implying a decrease in action potential duration induced by halothane (42,43) or enflurane (44) with an increase produced by isoflurane (41) and the increased QT intervals associated with all of these anesthetics observed in the present study. Alterations in the endogenous autonomic tone do not appear to be the modulating factor inasmuch as total autonomic nervous system blockade further increased the changes in QT interval and/or QT_c produced by the three anesthetics. Since the anesthetics have been postulated to alter multiple channel-mediated conductances, a difference in the bioavailability or concentration gradients of ionic species between in vitro and in vivo preparations might be responsible for the disparity in results. Multicellular preparations may develop accumulations or depletions of current-carrying ions at extracellular clefts that influence subsequent data interpretation (47,48).

Additionally, it has been established that profound differences exist between ventricular cells in terms of intrinsic, nonuniform action potential duration (49) and the susceptibility of such heterogeneous cells to pharmacologic agents that may alter action potential duration (50). Such differences may contribute to variability in results, because the QT interval represents a divergent population rather than individual ventricular cell responses.

Because the myocardium somewhat resembles an electrical syncytium (51), it is possible that disruption of this syncytium influences depolarization and/or repolarization responses of myocardial cells. Previous studies have demonstrated a relation between mechanical motion of the ventricle and the electrical activity of the heart (52) and an effect of ventricular stretch on action potential duration (53,54). Shorter action potentials have been observed during isometric versus isotonic contraction (52,53,55). A small reduction in afterload may increase the QT interval in an intact heart (56). Thus, systemic hemodynamic changes produced by the volatile anesthetics may have contributed to the prolongation of the QT interval in the present investigation.

The present results indicate that halothane in the presence of an intact autonomic nervous system prolongs the PR interval without a change in heart rate. Halothane has previously been shown to prolong the PR interval in the dog (57,58). Atlee et al. (57) have demonstrated halothane and enflurane to be equally depressant of AV nodal and His-Purkinje conduction times, the latter in contrast to our results; these investigators also found isoflurane to be least depressant. During inhibition of autonomic nervous system influences with atropine and propranolol, the anesthetics halothane, isoflurane, or enflurane were established to have no effect on specialized AV conduction times, a finding consistent with the present results (57).

In conclusion, the present investigation has shown that the volatile anesthetics halothane, isoflurane, and enflurane directly prolong the QT_c in the chronically instrumented dog independent of change in autonomic nervous system activity. In humans there exists a critical length of QT_c, and exceeding it increases the risk of development of ventricular ectopy. The observed changes in QT_c are most likely due to a prolongation of ventricular repolarization. Similar changes are shared by certain antiarrhythmic agents such as quinidine. Whether or not the effects of the volatile anesthetics on QT_c are additive with other congenital or acquired forms of QT_c prolongation has yet to be examined. The present results would indicate that caution should be observed during the

administration of volatile anesthetics to patients with abnormalities of QT interval.

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Lumbar Plexus Block in Children: A Comparison of Two Procedures in 50 Patients

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DALENS B, TANGUY A, VANNEUVILLE G. Lumbar plexus block in children: a comparison of two procedures in 50 patients. *Anesth Analg* 1988;67:750-8.

Two techniques for blocking the lumbar plexus were prospectively evaluated in 50 children undergoing surgery in the hip region and randomly allocated to one of two equal groups. A variant of the "psoas compartment block" and the classic technique were used in groups 1 (n = 25) and 2 (n = 25), respectively. All procedures were carried out under light general anesthesia with the patients in the lateral position using insulated needles and electrical stimulation. Both procedures were effective, allowing completion of surgery without additional treatment in almost all

*patients. However, the distribution of analgesia differed: 23 (ipsilateral) lumbar and sacral plexus blocks and 2 (ipsilateral) lumbar blocks alone were produced in group 2, compared to 22 areas of anesthesia comparable to those that might be associated with a lumbar epidural block and two ipsilateral lumbar plexus blocks in group 1. The two techniques are not, therefore, mere variants of the same basic approach to the lumbar plexus. The procedure described by Winnie et al. (*Anesthesiol Rev* 1974;1:11-6) was more suitable for providing unilateral blockade than the "psoas compartment block."*

Key Words: ANESTHETIC TECHNIQUES, REGIONAL—lumbar plexus block. ANESTHESIA—pediatric.

Regional anesthetic techniques for operations on the upper part of the lower extremities usually consist of either central blocks (epidural anesthesia especially, but also spinal) or multiple peripheral nerve blocks. There are disadvantages with both types of procedures. Bilateral blockade is unnecessary and undesirable for unilateral operations, but the performance of several peripheral blocks, while providing unilateral anesthesia, is time-consuming and may significantly increase the dangers of inaccurate injection and systemic toxicity.

To overcome these inconveniences, Winnie et al. (1) described the "3-in-1 block," a technique for blocking the three main nerves of the lumbar plexus with a single injection. Unfortunately, the femoral lateral cutaneous and also the obturator nerves may remain unaffected in a number of cases in which the 3-in-1 block is used. A direct approach to the lumbar plexus could be more appropriate, and two techniques have been described in adults (2,3).

We have reevaluated the gross anatomy of the lumbar plexus and found that both techniques could be safely performed in children provided the nerves could be precisely located by electrical stimulation as previously reported (4). After institutional approval, a prospective study was undertaken on 50 pediatric patients scheduled for operations on the upper part of the lower limb, with the aim of evaluating the ease and reliability of these two procedures in children.

Materials and Methods

Anatomic Considerations

The lumbar plexus is formed by the union of ventral rami of the first to fourth lumbar spinal nerves but usually also receives a twig from the twelfth thoracic nerve. The plexus lies within the substance of the psoas major muscle (Fig. 1), in a fascial plane termed the "psoas compartment" by Chayen et al. (3). This compartment is bordered by 1) the posterior mass of the muscle attached to the transverse processes of lumbar vertebrae and, 2) the anterior mass attached to the intervertebral disks and lips of lumbar vertebral bodies.

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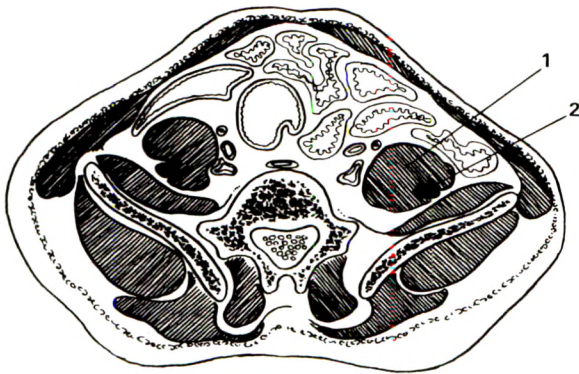


Figure 1. Cross-section of the trunk at the L-5 level. 1, Psoas muscle; 2, lumbar plexus within the substance of the Psoas muscle.

The three main nerves of the lumbar plexus that supply the lower limb emerge from the Psoas compartment at different levels of the muscle (Fig. 2):

- At the upper part of the lateral border of the compartment, the lateral cutaneous nerve of the thigh exists.
- At the union of the middle and lower thirds of the lateral border of the compartment, the femoral nerve emerges.
- At the medial border of the compartment, near the pelvic brim, the obturator nerve exists.

The iliac fascia covers both the Psoas and iliacus muscles and, after their emergence from the Psoas major muscle, the branches of the lumbar plexus. These nerves remain posterior to the iliac fascia, whereas the iliac vessels run anterior to it.

The sacral plexus is ensheathed by expansions of the fascia of the piriformis muscle. This fascia is (indirectly) continuous with that covering the obturator internus muscle (5) and, because the latter is continuous with the iliac fascia, it may be expected that a sufficient volume of fluid injected below the iliac fascia could spread until it reached the fascia of the piriformis muscle (and the sacral plexus). However, the precise relations of these fascias have not been well explored.

Materials

Fifty ASA 1 children, 22 female and 28 male, scheduled for operations on the hip and the upper part of the lower limb (Table 1), were selected after informed consent had been obtained from parents and, as often as possible, from the children themselves. The patients ranged in age from 7 months to 16 years and in weight from 8 kg to 52 kg. They were randomly allocated to one of two equal groups differing from one

another in the technique used for blocking the lumbar plexus nerves. A modification of the Psoas compartment block as reported by Chayen et al. (3) was used in group 1, whereas the lumbar plexus block technique of Winnie et al. (2) was used in Group 2.

Methods

Anesthetic procedures. All procedures were carried out in operating rooms under light general anesthesia (without tracheal intubation) after insertion of a peripheral venous line, as is usual in our unit for regional block procedures in children (6,7). All patients were given 0.02 mg/kg atropine and 0.05–0.1 mg/kg diazepam IV. Anesthesia was induced using either halothane (in 65% N₂O/35% O₂) or intravenous thiopental (4 mg/kg) as preferred by the children. Anesthesia was maintained using 0.25–0.5% halothane in 65% N₂O/35% O₂.

We used 22-gauge insulated needles, 50-mm long in children under 10 years of age and 100-mm long in older patients, and a nerve stimulator (Myotest from Datex) adjusted to deliver a 2-mA impulse every second. Patients were placed in the lateral position with the side to be blocked lying uppermost. The posterior superior iliac spine was marked on the skin, and the intercrystal line was drawn from ipsilateral to contralateral upper borders of the iliac bone.

In group 1 ($n = 25$), the spinous process of the fifth lumbar vertebra was located, and the site of puncture was marked on the skin at the midpoint of the line extending from this spinous process to the posterior superior iliac spine (Fig. 3A). (The site of puncture was modified from that recommended by Chayen et al. [3] after anatomical evaluation in children of various ages.)

In group 2, the site of puncture was marked on the skin at the intersection of the intercrystal line with a perpendicular dropped from the posterior superior iliac spine (Fig. 3B), as recommended by Winnie et al. (2).

In both groups, the skin was cleaned and draped, and the needle was inserted at a right angle to the skin until it elicited twitches in the thigh. If either the iliac bone or the vertebral body of the fifth lumbar vertebra was contacted a few millimeters beyond the skin, the needle was withdrawn and reinserted either more medially or laterally. If twitches were not elicited after two attempts, a loss-of-resistance technique was used as recommended (3).

After aspiration was negative and after injection of a test dose (0.5–1 ml), the appropriate volume of anesthetic mixture was injected over 60–90 seconds.



Figure 2. Dissection of the lumbar region. Note the emergence of the nerves from the psoas major muscle. 1, Obturator nerve; 2, psoas muscle; 3, lateral cutaneous nerve of the thigh; 4, femoral nerve.

The patient was then placed in the dorsal recumbent position for 10 minutes before surgery.

One of the following two anesthetic solutions was elected according to the expected duration of surgery and the need for postoperative analgesia:

- A mixture of equal volumes of 0.5% bupivacaine and 1% etidocaine, both with 1:200,000 epinephrine.
- A solution of 1% lidocaine with 1:200,000 epinephrine. (Two patients in group 1 and one in group 2 received a mixture of equal volumes of 2% lidocaine with epinephrine and Iopamiron 200, a contrast agent suitable for myelographies.)

The solutions were administered on a weight basis: .75 ml/kg up to 20 kg, 20 ml for 20–30 kg, and 25 ml or 30–55 kg.

Monitoring procedures and evaluation of anesthesia. Electrocardiogram tracings, respiratory rate, blood pressure (Dinamap), tidal volume, and end-tidal CO₂ were monitored during the procedures. The block

Table 1. Surgical Indications

Indications	Group 1 <i>n</i> = 25	Group 2 <i>n</i> = 25
Osteotomies of the femur	12	10
Arthrotomies of the hip	5	4
Removal of implants	5	7
Wounds and skin grafts of the thigh	3	4

was considered successful when the scheduled operation could be achieved without any additional treatment. When either intravenous narcotics or increased concentrations of halothane became necessary, regional anesthesia was considered unsuccessful.

The extent of analgesia was evaluated after completion of surgery by skin pinching. Analgesia was considered complete when the patient did not complain of pain while sustained pinching was applied. It was considered incomplete when the child either felt pinching as unpleasant (but not painful) or, in the very youngest, reacted in a way different from that when adjacent anesthetized areas were pinched.

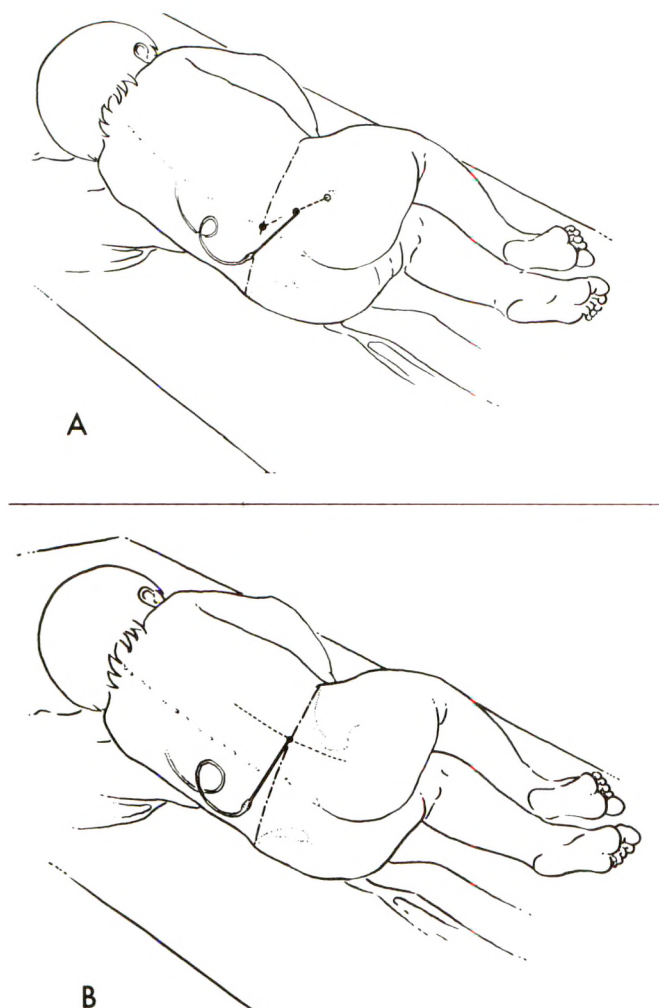


Figure 3. Landmarks and site of puncture. (A) Group 1; (B) Group 2.

Statistical methods. Data from the two groups were compared using the Mann-Whitney test (measurable parameters) and the χ^2 test (qualitative parameters). Differences were considered significant at $P < 0.05$.

Results

The two groups were similar in regard to age, weight, indication, and duration of surgical procedures, and no complications were observed (either during the procedures or later).

Group 1

Difficulties in inserting the needle were encountered in seven cases: The needle had to be inserted more

medially in two cases and more laterally in five cases. Twitches were elicited in 24 of the 25 patients, on the first attempt in 19 patients, and on the second attempt in the remaining 5.

In 22 of the 24 patients in whom twitches were elicited, the twitches involved muscles of the thigh as well as those of the leg and foot (especially flexion-extension movements of the ankle and toes); in these 22 patients the twitches disappeared by the time 0.5 ml of the anesthetic solution had been injected. In two patients, the twitches were elicited only in the thigh, and more than 2 ml of the anesthetic solution was injected before they disappeared. The depth at which the needle was inserted is shown in Fig. 4A.

In all 24 of the patients in whom twitches were elicited, anesthesia was successful, allowing completion of surgery without additional treatment. The loss-of-resistance technique was employed for the one remaining patient, but this proved unsuccessful. The distance between the skin and the site at which the injection was made in this patient was significantly less than that expected from the depth-age curve established in the 24 other patients of the group.

The two patients in whom twitches were elicited only in muscles of the thigh developed complete sensory blockade in the areas supplied by the femoral lateral cutaneous and obturator nerves, while the areas supplied by the posterior femoral cutaneous and sciatic nerves remained unchanged. The 22 patients in whom twitches were elicited both in the thigh and in the distal part of the lower limb showed evidence of epidural anesthesia; not only ipsilateral lumbar and sacral plexus nerves were anesthetized, but also those from the contralateral side, and the upper limit of anesthesia was located between T12 and T7 dermatomes. Complete motor blockade developed in the seven patients who received etidocaine.

The epidural spread of the anesthetic solution was confirmed by X-ray films (Fig. 5) in two patients in whom contrast material was injected. (X-rays were performed before surgery for precise location of implants to be removed.)

Group 2

In this group, no difficulties were encountered for insertion of the needle, and twitches were elicited in all 25 patients, on the first attempt in 22 cases and on the second attempt in the other 3. (No loss-of-resistance technique was used in this group.) In all cases, the twitches were elicited in muscles of the thigh only, and they disappeared before the injection

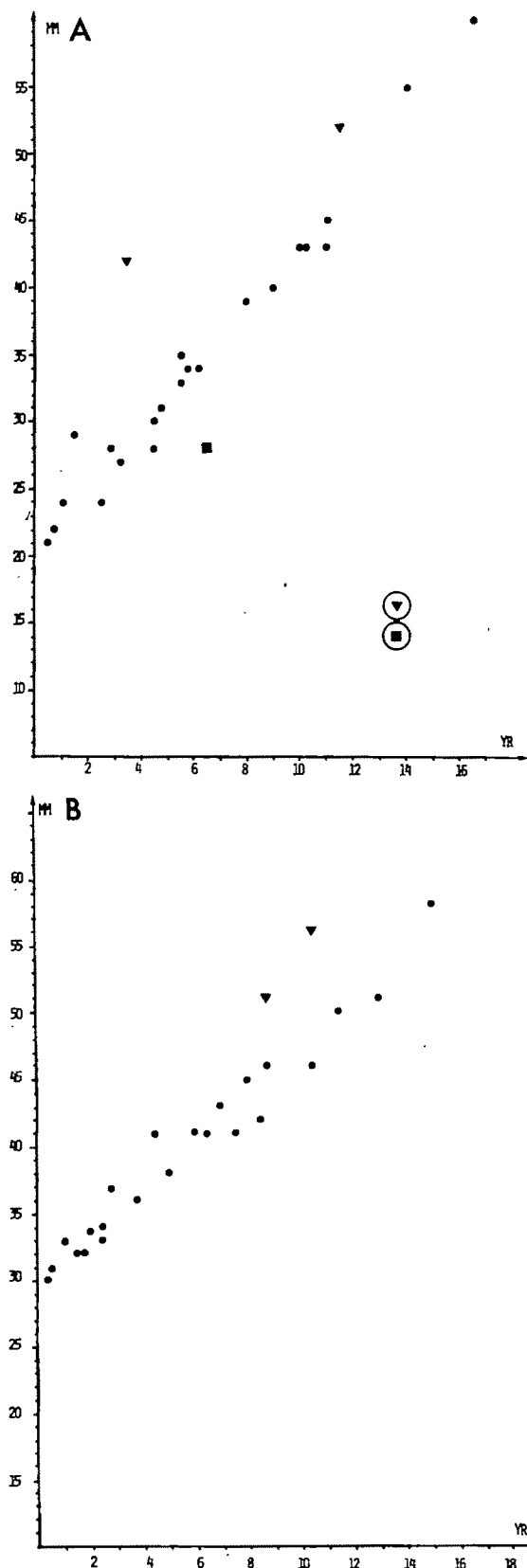


Figure 4. Depth at which the block needle was inserted. (A) Group 1. (○) epidural anesthesia; (△) block of lumbar nerves solely; (□) failure of the block. (B) Group 2. (△) block of lumbar plexus nerves solely; (○) block of lumbar and sacral plexus nerves.

of 0.5 ml of the anesthetic solution. The procedure was successful in all 25 patients. The depth at which the needle was inserted is shown in Figure 4B.

The anesthetized area was that supplied by 1) all sensory nerves issuing from the lumbar plexus in all 25 patients and, 2) the posterior femoral cutaneous and the sciatic nerves in 23 of the 25 patients. The sensory blockade of skin areas supplied by the sacral plexus was complete in 18 and incomplete in 4 cases (out of the 23 patients in whom sciatic nerve block developed). No complete motor blockade was observed in areas supplied by the sciatic nerve, while a complete motor block was found in areas supplied by the lumbar plexus in the eight patients given etidocaine. A radiographic evaluation of the spread of the anesthetic solution is shown in Figure 6.

Comparison of the Two Groups

We found the technique of Winnie et al. (2) easier than that modified from Chayen et al. (3), but the success rate of both procedures was high (no failure when twitches were elicited). The depth at which the lumbar plexus was located was significantly greater (by 6–10 mm) in group 2 than in group 1, and the distribution of analgesia was totally different ($P < 10^{-6}$) in the two groups: 22 areas of anesthesia involving the two lower extremities and the lower part of the trunk (i.e., a distribution of anesthesia comparable to what might be associated with an epidural blockade), 2 lumbar plexus blocks, and 1 total failure in group 1, compared to 23 ipsilateral lumbar plus sacral plexus blocks, 2 ipsilateral lumbar plexus blocks solely, and no complete failure in group 2.

Discussion

The use of a nerve stimulator for locating the plexus nerves proved to be reliable with both techniques used in this study, since complete sensory blockade was produced in areas supplied by the lumbar plexus in all patients in whom twitches were elicited in the lower limb (Table 2). From a technical point of view, the approach to the lumbar plexus was easier with the technique of Winnie et al. (2) used in group 2 than with that of Chayen et al. (3) used in group 1.

The most surprising (and unexpected) finding of this comparative study pertains to the distribution of anesthesia. The two techniques do not represent variants of the same basic approach to the lumbar plexus. In fact, the technique of Winnie et al. (2) is

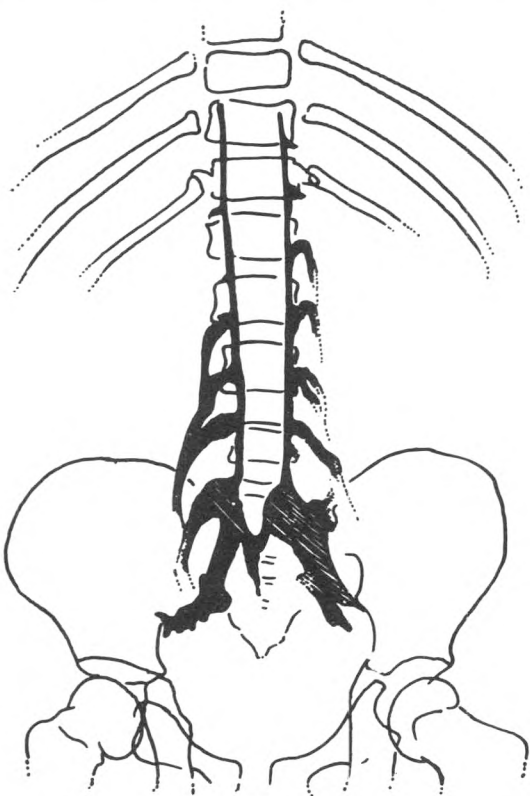


Figure 5. Epidural spread of the solution (patient from group 1). (A) Front view; (B) lateral view.

fundamentally a peripheral plexus nerve block technique, whereas that modified from Chayen et al. (3) is basically a central block technique, because it pro-

duced bilateral blockade of the lower part of the trunk and the lower extremities in 22 of 25 procedures.

In group 1, twitches were elicited not only in the

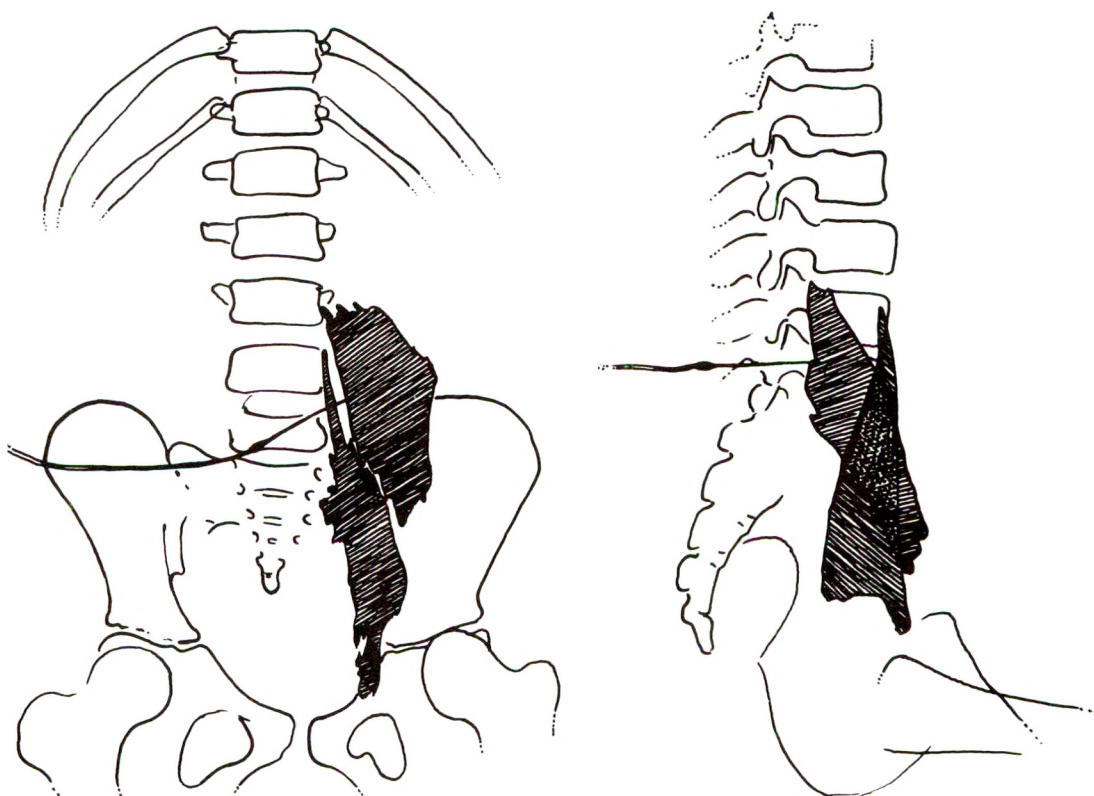
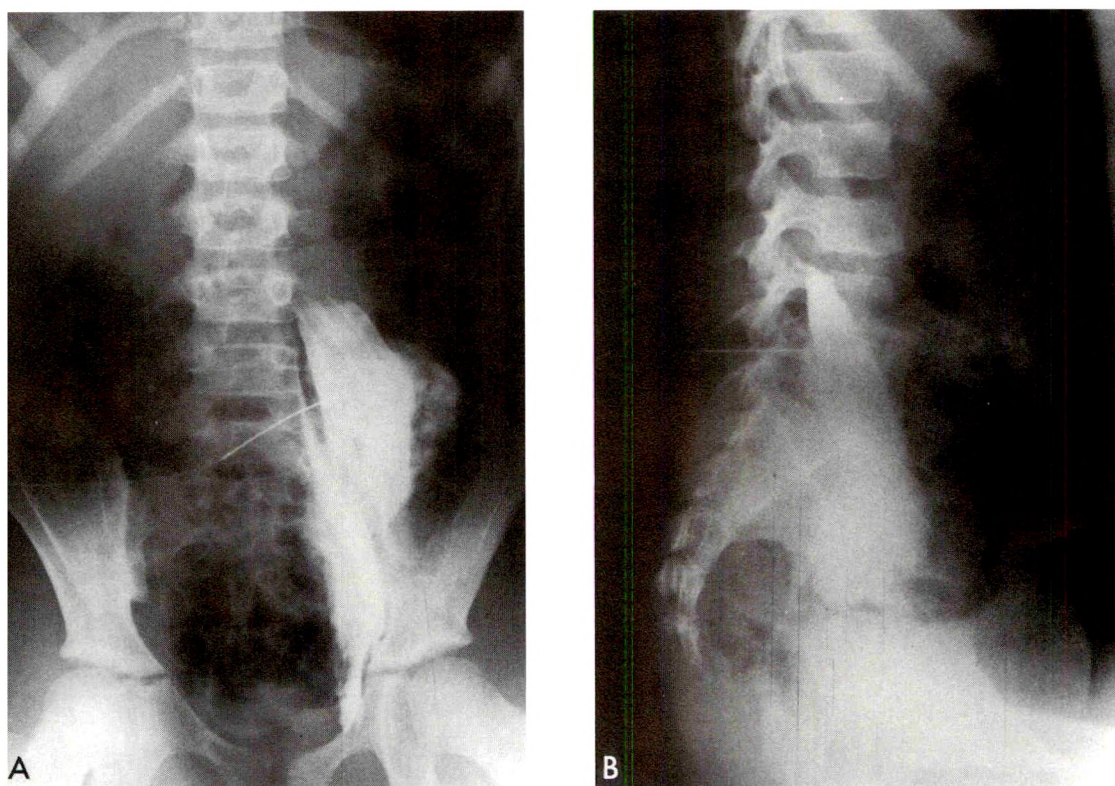


figure 6. Spread of the solution in a patient from group 2. The ischia iliaca and the fascia of the obturator internus muscle are largely invested by contrast material. (A) Front view; (B) lateral view.

thigh but also in the leg and foot. Due to the position of the site at which the needle was inserted and the direction in which it was inserted, it is likely that the tip of the needle was placed close to the lumbosacral

Table 2. Evaluation of the Efficacy of Two Techniques for Lumbar Plexus Block

	Group 1 <i>n</i> = 25	Group 2 <i>n</i> = 25
Location of Trunks	24	25
On first attempt	13	22*
On second attempt	11	3*
Same site of puncture	5	3
Different site	7	0*
Twitches elicited	24	25
In thigh only	2	25*
In thigh, ankle, and foot	22	0*
No twitches elicited	1	0
Success rate	96%	100%
Distribution of analgesia		
Lumbar plexus solely	2	2
Lumbar and sacral plexuses	0	23*
Epidural anesthesia	23	0*

*Significant difference at level $P < 0.05$.

trunk (a root of the sciatic nerve). It has been reported that the epidural space may extend far beyond intervertebral foramina, along spinal nerves (8,9). Therefore, it may be presumed that the needles could have entered such epidural extensions. However, this hypothesis does not account for all 22 patients of group 1 who developed epidural anesthesia. Muravchick and Owens (10) have reported a case of (probable) epidural spread of local anesthetics after lumbar plexus block at the L4–5 level (a higher level than in group 1) and at a distance of 5 cm from midline (i.e., even more laterally than in our patients). These present data bring into question the precise limits of the epidural space at lumbar levels.

In their original report, Chayen et al. (3) did not observe epidural spread of the anesthetic solution, and the distribution of anesthesia did not extend beyond the lumbar plexus. This appears surprising when compared to the observations of Winnie et al. (2); as in our group 2, Winnie et al. (2) found that both sacral plexus and lumbar plexus nerves were anesthetized even though the block needle had been inserted laterally, at the L4–5 level, i.e., at a greater distance from the sacral plexus than in the technique used in our group 1. However, the depth to which Chayen et al. (3) inserted the block needle (12 cm usually) appears excessive: the roots of the lumbar plexus emerge from intervertebral foramina and, due to the disposition of the psoas major muscle, it is unlikely that the psoas compartment lies more than 20–25 mm deeper than the distance between skin and ligamentum flavum at the midline. Thus it may be supposed that the tip of the needle was not placed between the anterior and posterior masses of the psoas major muscle, but instead between the anterior

mass and the iliac fascia. The anesthetic solution may thus have spread along the anterior aspect of this fascia, then contacting the lateral cutaneous, femoral, and obturator nerves at their emergence from the substance of the psoas muscle. In such an event, the technique may have produced a peripheral blockade of the three main nerves of the lumbar plexus instead of a true lumbar plexus block. Such a situation may have occurred in the two patients in group 1 in whom the distribution of anesthesia was limited to the areas supplied by lumbar plexus nerves. The depth at which the needle was inserted was significantly greater in these 2 patients than in the 22 who developed bilateral sensory blockade.

The loss-of-resistance procedure was unsuccessful in the one case in which it was used; in this patient, the depth to which the needle was inserted was less than that expected from our data (when twitches were elicited). It may be supposed that the needle was inserted beyond the quadratus lumborum muscle but immediately above the posterior surface of the fascia iliaca. In this event, the anesthetic solution would presumably spread at the outer surface of the iliac fascia, thus not contacting the lumbar plexus nerves that run at the inner surface of the fascia.

The path followed by the anesthetic solution in reaching the sacral plexus is not readily evident. It may be that the psoas compartment is a low-pressure compartment and that the injected solution may reach the lower part of the medial border of the psoas muscle, and then the sacral plexus, by successively investing the fascia of the obturator internus, then that of the piriformis muscles. The radiographic findings of Figure 6 are consistent with this hypothesis. This absence of epidural spread is remarkable in group 2 as compared to group 1, but further evaluations on larger series are desirable.

In any case, the two techniques used for approaching the lumbar plexus are not equivalent in pediatric patients, and the one used in group 1 should be considered as a central block procedure. This is not necessarily disadvantageous, and psoas compartment blocks may even represent a useful alternative procedure to lumbar approaches to the epidural space, for example, in patients with severe spine deformities, because vital organs including aorta, vena cava, kidney, or abdominal viscera can be avoided as long as excessive depth of insertion of the needle is avoided.

However, within the initial scope of this study, i.e., selecting the most appropriate single-shot technique for unilateral blockade of lumbar plexus

nerves, the technique of Winnie et al. (2) appears to be the more suitable.

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Sixty-Two Years Ago In

Anesthesia & Analgesia

H. W. Haggard: The absorption, distribution and elimination of anesthetics. Current Researches in Anesthesia & Analgesia 1926;15:1-7.

While Assistant Professor of Applied Physiology at Yale, Haggard never heard the word *pharmacokinetics*. He became, however, one of the first pharmacokineticists when he established the principles of the uptake, distribution, and elimination of inhalation anesthetics. Yes, John Snow in the 1840s and '50s was somewhat of a pharmacokineticist, but this paper by Haggard and preceding papers by him in the *Journal of Biological Chemistry* (1924;59:737-802) describe with exquisite accuracy and detail matters such as determinants of anesthetic tension, partial pressures and equilibrium, quantitative aspects of anesthetic uptake, concentrations of anesthetics in the brain, utility of carbon dioxide, and "de-etherization." It is a humbling but infinitely rewarding experience to read Haggard's papers, not just this and his 1924 articles, but also his 1940 editorial on "The place of the anesthetist in American Medicine" that appeared on page 1 of volume 1 of that new journal, *Anesthesiology*.

Hyperkalemia after Dantrolene and Verapamil-Dantrolene Administration in Dogs

Alberto C. San Juan, Jr, MD, K. C. Wong, MD, PhD, and J. David Port, BS

SAN JUAN AC JR, WONG KC, PORT JD. Hyperkalemia after dantrolene and verapamil-dantrolene administration in dogs. *Anesth Analg* 1988;67:759-62.

The concurrent administration of dantrolene and verapamil has the theoretical advantage of being more efficacious than dantrolene alone in the treatment of malignant hyperthermia. However, the combination has been reported to cause fatal hyperkalemia in pigs. The present study evaluated the serum concentrations of cations, serum osmolality, and cardiovascular responses in 20 mongrel dogs after dantrolene with and without the concurrent administration of verapamil. The dogs were randomly classified into four groups of five dogs each: group 1 received neither dantrolene nor verapamil; group 2 received three successive intravenous doses of dantrolene (1, 3, and 6 mg/kg) at 30-minute intervals; group 3 received verapamil 0.1 mg/kg IV bolus, followed by a continuous infusion of $5 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{hr}^{-1}$; and group 4 received verapamil as in group 3, followed by dantrolene as in group 2. Measurements were made at 15-minute intervals for $2\frac{1}{2}$ hours. Progressive and similar

statistically significant increases in mean serum potassium occurred after 105 minutes in dogs given dantrolene (group 2, mean peak serum potassium levels 5.4 ± 0.5 mmol/L) and after 90 minutes in dogs given verapamil-dantrolene (group 4, 5.2 ± 1.6 mmol/L). A statistically significant decrease in serum sodium levels was also found in groups 2 and 4. One dog in group 4 developed intermittent second-degree heart block after the final dose of dantrolene. Serum calcium levels (ionized and total) tended to decrease in groups 2 and 4. There were no statistically significant differences in osmolalities, cardiac outputs, or mean arterial blood pressures among groups. In summary, significant elevations of serum potassium were observed in this dog model given dantrolene with and without verapamil. However, the increase in serum potassium was no greater with dantrolene plus verapamil than it was with dantrolene alone.

Key Words: IONS—potassium, hyperkalemia. PHARMACOLOGY; DRUG INTERACTIONS—dantrolene, verapamil. HYPERTHERMIA, MALIGNANT—dantrolene, verapamil.

Dantrolene is currently the only drug used for the treatment of malignant hyperthermia (1-3). Its high lipid solubility enables it to cross muscle cell membranes easily. The drug inhibits intracellular calcium release by the sarcoplasmic reticulum and dissociates excitation-contraction in muscle cells (4). Dantrolene has no depressant effects on the cardiovascular system in anesthetized dogs and sheep (5-7) but has been shown to depress contractility of isolated cardiac tissue (8,9).

Verapamil, a calcium entry blocking agent, is useful in treating supraventricular arrhythmias (10). The

hemodynamic effects of the drug depend on the direct effects and reflex responses in the intact animal (11). Verapamil has been shown to attenuate the malignant hyperthermia syndrome in susceptible pigs.

Because the etiology of malignant hyperthermia is believed to be the result of abnormal release of calcium by intracellular sarcoplasmic reticulum, a reduction in calcium entry into the cell should help to reduce intracellular $[\text{Ca}^{2+}]$. Thus, verapamil in combination with dantrolene has been suggested as being possibly more efficacious than dantrolene alone in the treatment of malignant hyperthermia. Such a combination, however, has been reported to cause cardiovascular depression in dogs (12) and hyperkalemia with cardiovascular collapse in pigs (13). The purpose of this study was to ascertain whether these responses observed in pigs could be similarly elicited in dogs. Because cardiovascular function depends on

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proper ionic concentrations of several cations in the extracellular compartment, and not solely on potassium concentration, we measured the concentrations of serum cations, serum osmolarity (osm), and cardiovascular parameters in dogs given dantrolene with and without concurrent verapamil administration.

Methods

This study was approved by the University of Utah Animal Research Committee. Twenty mongrel dogs, weighing 17.5 ± 3.1 kg (mean \pm SD), were anesthetized with thiopental 20 mg/kg IV. After tracheal intubation the lungs were mechanically ventilated to maintain P_{aCO_2} between 30 and 40 mm Hg. Anesthesia was maintained using a 10% α -chloralose-urethane solution (100 mg/kg IV bolus followed by a $10 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ infusion). A femoral arterial catheter was inserted and a 7F Swan-Ganz thermodilution catheter (American Edwards Laboratories) was floated into the pulmonary artery via the external jugular vein to measure central venous (CVP), pulmonary artery (PA), and pulmonary artery wedge (PAWP) pressures and cardiac output (CO) (Edwards Laboratories 9520A). Cardiac output measurements were done in triplicate and determined at end-exhalation. Lead II of the ECG was recorded at 25 mm/sec. Heart rate (HR) and PR, QRS, and QT intervals were measured. A warming blanket was used to maintain normothermia ($37.8 \pm 1.0^\circ\text{C}$). Serum $[\text{Na}^+]$, $[\text{K}^+]$, and $[\text{Ca}^{2+}]$ (ionized) were measured (NOVA Biomedical 1 and 2). Total calcium was determined using the ADAM (Hitachi 737). Serum osmolarity was measured with the Wescor vapor osmometer (model 5100 C). Arterial pH, P_{aO_2} , P_{aCO_2} , and base excess were also measured (Radiometer Copenhagen ABL 1). All cardiovascular and blood chemistry measurements were made every 15 minutes.

All drugs were dissolved in sterile water, and normal saline was infused at approximately $5 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$ during the study. After a 1-hour stabilization, two baseline measurements were obtained 15 minutes apart. The dogs were then randomly classified into four groups of five dogs each. Group 1 received neither dantrolene nor verapamil. Group 2 received three successive IV doses of dantrolene (1, 3, and 6 mg/kg infused over 10 minutes) at 30-minute intervals. Group 3 received verapamil 0.1 mg/kg IV bolus followed by a continuous infusion of $5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{hr}^{-1}$. Group 4 received verapamil as in group 3, followed by dantrolene as in group 2. Measurements were obtained at 15-minute intervals for 2 $\frac{1}{2}$

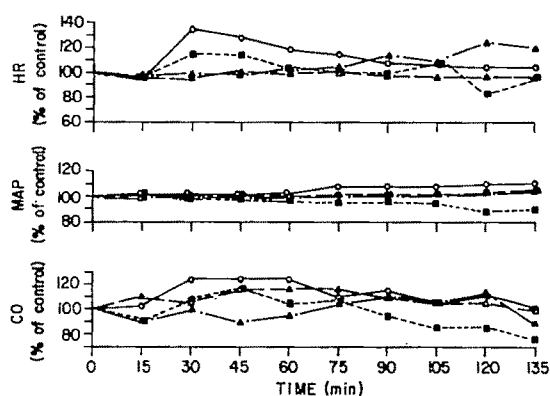


Figure 1. Hemodynamic data. (Δ) Group 1, control; (\blacktriangle) group 2, dantrolene alone; (\circ) group 3, verapamil alone; (\blacksquare) group 4, verapamil-dantrolene. Each point represents the mean of five dogs. Verapamil infusion was initiated at time 15 minutes, whereas dantrolene doses were given at 45, 75, and 105 minutes.

hours. Analysis of variance for repeated measurements and an unpaired *t*-test were used to analyze the data. Results are expressed as means \pm SD. $P < 0.05$ was considered significant.

Results

Heart rate, mean arterial pressure, and cardiac output were not statistically significantly different between groups throughout the study (Fig. 1). Pulmonary vascular resistance and systemic vascular resistance did not differ between groups. One dog in group 4 developed intermittent second-degree heart block with a junctional rhythm after the final dose of dantrolene. PR, QT, and QRS durations were similar in all groups. All dogs survived the study protocol.

There were also no significant changes in or differences in blood gas tensions, pH, or base excess between groups. Serum total calcium levels were significantly lower in group 4 at 120 and at 135 minutes than that in groups 1 and 3 at 120 minutes and in group 1 at 135 minutes (Fig. 2). Mean $[\text{Ca}^{2+}]$ level in group 2 was significantly lower than in group 3 at 120 minutes (Fig. 2). Differences were statistically insignificant at 135 minutes. Serum osmolarities (298 ± 32.7 mmol/L) did not change within groups or differ between groups at any time during the study.

Mean study $[\text{Na}^+]$ levels at 120 minutes in groups 2 and 4 were significantly lower than those in groups 1 and 3. At 135 minutes, the serum $[\text{Na}^+]$ levels in groups 2 and 4 continued to be significantly lower than Na^+ concentrations in groups 1 and 3 (Fig. 3).

A progressive increase in mean serum $[\text{K}^+]$ starting after about 70 minutes is evident in the dogs given dantrolene (group 2) and verapamil-dantrolene

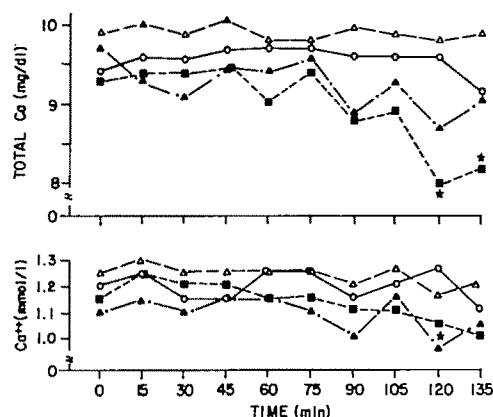


Figure 2. Serum total and ionized calcium concentrations in groups 1-4 (symbols as in Figure 1). (*) Significant at $P < 0.05$.

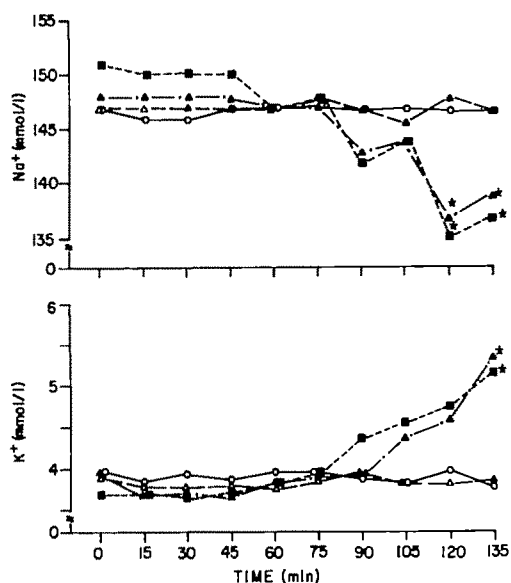


Figure 3. Mean serum [Na] and [K] in groups 1-4 (symbols as in Figure 1). (*) Significant at $P < 0.05$.

(group 4). While $[K^+]$ increased in group 2, the increase was not statistically different between groups 2 and 4; i.e., dantrolene versus dantrolene plus verapamil. The dogs given α -chloralose-urethane only (group 1) and verapamil alone (group 3) did not have any significant elevation of serum $[K^+]$ levels.

Discussion

Our study shows that cumulative doses of dantrolene alone and in combination with verapamil are associated with an elevation of serum $[K^+]$ in dogs. Hyperkalemia with verapamil-dantrolene combination has been previously reported in swine (13). However, we found that the increase in $[K^+]$ can be totally

attributed to intravenous dantrolene alone in our dog model.

Preinduction levels of serum $[K^+]$ have been reported to be increased in humans given dantrolene orally to reduce muscular fasciculation due to succinylcholine (14). Marked elevations in serum potassium were also reported in a patient who received verapamil and dantrolene (15). The same patient had a mildly increased serum $[K^+]$ level after pretreatment with nifedipine and dantrolene for a second operative procedure. Saltzman et al. (13) found slight but insignificant increases in potassium levels in swine given dantrolene alone. In contrast to the latter study, we found significant elevations in serum $[K^+]$ in the dog after incremental doses of dantrolene, suggesting species difference to dantrolene administration.

Verapamil, a calcium channel blocker, has negative dromotropic, chronotropic, and inotropic effects, which contribute to its antiarrhythmic effect in vivo (12). Hyperkalemia, in a concentration-related manner, can produce AV conduction block, AV dissociation, and myocardial standstill. Marked hyperkalemia and verapamil has caused cardiovascular collapse in pigs (13). Myocardial depression in dogs given verapamil-dantrolene combination has been reported by Lynch et al. (12). The latter investigators did not measure serum potassium levels. In contrast to the previous studies, we did not find significant cardiovascular depression in our study. The difference may be attributed to the higher cumulative doses of verapamil (up to 0.6 mg/kg) used by Lynch et al. (12) in addition to larger doses of the basal anesthetic drugs (α -chloralose 40-80 mg/kg and urethane 400-800 mg/kg). Another factor may be the slower increase in serum $[K^+]$ in our dog model. Our doses of verapamil and dantrolene were similar to those used by Saltzman et al. (13) in swine. Saltzman et al. reported an elevated mean serum potassium level (8.0 mmol/L) within 2 hours of the start of their study. Our final serum $[K^+]$ determinations at 135 minutes were 5.4 and 5.2 mmol/L in groups 2 and 4, respectively. Had we extended the duration of our study, it is possible that we would have seen myocardial depression from higher potassium levels and poor cardiovascular tolerance by verapamil-pretreated dogs.

We found AV conduction abnormalities, specifically intermittent second-degree heart block with junctional rhythm, in a dog given dantrolene after a verapamil pretreatment. Similar findings were reported by Lynch et al. (12) and Saltzman et al. (13).

Less KCl is required to elevate serum potassium levels after verapamil (15). It has been postulated that verapamil impairs compensatory mechanisms for

controlling extracellular $[K^+]$. Verapamil did not alter succinylcholine-induced increase in serum $[K^+]$ in dogs (16). However, a single dose of dantrolene (100–150 mg) given 2 hours preoperatively has been found to reduce the succinylcholine-induced hyperkalemia and muscular fasciculation (14).

The decrease serum $[Na^+]$ in dogs given dantrolene and verapamil–dantrolene could be attributed to expansion of intravascular volume and subsequent hemodilution. Each 20-mg vial of dantrolene sodium is reconstituted with 60 ml sterile water before IV administration. A 10 mg/kg dose of dantrolene in a 20-kg dog provides a fluid load of 600 ml sterile water. Mannitol (3 g in a 20-mg vial of Dantrium), an osmotic diuretic, renders the reconstituted drug isotonic. Mannitol expands plasma volume by absorbing extravascular water. The fluid load and mannitol could contribute to the hyponatremia in dogs that received dantrolene and the combination regimen. However, in spite of the apparent hemodilution, serum $[K^+]$ increased in dogs that received the above drug regimen. The lower total serum $[Ca^{2+}]$ levels evident in dogs given the verapamil–dantrolene combination cannot be attributed to hemodilution alone, because there were no significant changes in those given dantrolene only. We postulate that the more marked decrease in total $[Ca^{2+}]$ levels in the dogs given verapamil–dantrolene may be due to impairment of physiologic mechanisms regulating extracellular calcium. Although the reductions in serum $[Ca^{2+}]$ (total and ionized) and $[Na^+]$ were statistically significant, they were probably not physiologically significant (Fig. 2). More severe levels of hypocalcemia and hyponatremia can produce well-known cardiac arrhythmia and negative inotropic effects.

In conclusion, we observed that dantrolene with and without verapamil produced statistically significant but equal elevations of serum $[K^+]$ in our dog model. Because there was no quantitative difference in the level of hyperkalemia, verapamil did not potentiate the hyperkalemic effect of dantrolene in dogs as previously reported in swine (13). Both verapamil and hyperkalemia have well-known negative chronotropic and dromotropic effects, which have been shown to produce myocardial depression in experi-

mental animals (12,13) and in a patient (14). However, no hemodynamic depression was observed among the groups in the present study.

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The Effect of Pleural Pressure on the Hypoxic Pulmonary Vasoconstrictor Response in Closed Chest Dogs

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CHEN L, WILLIAMS JJ, ALEXANDER CM, RAY RJ, MARSHALL C, MARSHALL BE. The effect of pleural pressure on the hypoxic pulmonary vasoconstrictor response in closed chest dogs. *Anesth Analg* 1988;67:763-9.

The effect of intrapleural pressure on the hypoxic pulmonary vasoconstrictor (HPV) responses to atelectasis and hypoxia were measured in two groups of anesthetized closed chest dogs. The right lung was continuously ventilated with 100% O₂. The left lung was initially ventilated with 100% O₂ (hyperoxia) but subsequently underwent either reabsorption atelectasis (atelectasis; group I) or ventilation with a hypoxic gas mixture (hypoxia; group II). The mean intrapleural pressure in the left hemithorax was 5.4 cm H₂O during hyperoxia, but with left lung atelectasis decreased significantly to -3.8 cm H₂O by 15 minutes and to

-4.2 cm H₂O by 90 minutes. Venous admixture (%VA) increased significantly from 10.3% during hyperoxia to 33.2% at 15 minutes of left lung atelectasis and to 34.6% at 90 minutes. However, after sternotomy with the left lung still atelectatic, the %VA decreased significantly to 25.4%. For the hypoxia group, %VA increased significantly from 9.2% during hyperoxia to 29.9% at 15 minutes of left lung hypoxia and 25.1% at 90 minutes. HPV diverted blood flow away from both atelectatic lung and hypoxic lung. However, due to the negative intrapleural pressure generated during left lung resorption atelectasis when the chest was closed, HPV was less effective during atelectasis than during hypoxia.

Key Words: LUNG, ATELECTASIS—hypoxic pulmonary vasoconstriction. HYPOXIA—pulmonary vasoconstriction.

Hypoxic pulmonary vasoconstriction (HPV) causes a diversion of blood flow from lung regions exposed to either atelectasis or hypoxic ventilation in open chest dogs (1-3). However, in closed chest animals, diversion of perfusion away from the collapsed lung may not occur; the ineffectiveness of the hypoxic pulmonary vasoconstrictor mechanism under these conditions has been attributed to the effects of changes in pleural pressure and/or lung volume on the blood vessels in collapsed lung (4), in inflated lung (5-7), and in isolated dog lung lobes (8). The present study examines hypoxic pulmonary vasoconstrictor responses in the intact closed chest dog in the absence of surgical thoracotomy and vessel manipulation.

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Methods

Anesthesia and Surgery

This study was approved by the University of Pennsylvania Animal Care and Use Committee. Twelve female dogs of mixed breed weighing 20.9 ± 0.8 kg were anesthetized with 30 mg/kg IV pentobarbital supplemented with 25-50 mg every 30 minutes. The dogs were placed in a supine position. The trachea was intubated with a 10-mm cuffed endotracheal tube, and mechanical ventilation was initiated. Muscle paralysis was established with 0.05 mg/kg IV pancuronium supplemented with 0.2-0.5 mg every 30 minutes. After subcricoid tracheostomy and placement of a double-lumen Kottmeier endobronchial tube (Rüsch, Inc.), the lungs were ventilated synchronously with humidified 100% O₂ via a dual-piston respirator (Harvard Apparatus Respiration Pump, model 618). Separation and isolation of the right and left lungs were determined by auscultation and by adding inspired helium to the right lung and demonstrating with a helium analyzer (Godart model 113)

that no cross contamination of the left lung occurred. Ventilation was adjusted to a tidal volume of approximately 25 ml/kg at a rate of 10 breaths/min to obtain equal peak airway pressures in each lung (15–20 cm H₂O). Expired gases flowed through a gas mixing cone before venting to atmosphere via an underwater seal providing the 2–5 cm H₂O PEEP. To maintain end-tidal and arterial P_{CO₂} close to 35–40 mm Hg, inspired CO₂ and/or the respiratory rate were adjusted. Each piston of the Harvard ventilator was part of a separate gas circuit with its gas composition determined by separate flow meters. After 100% O₂ ventilation, resorption atelectasis was obtained by occluding the left side of the double-lumen tube.

A peripheral vein was cannulated, and Normosol-R (Abbott Laboratories) was administered at rates estimated to be sufficient to maintain euvoemia (100–250 ml/hr). A Foley catheter was inserted to measure urine output. Body temperature was measured via a thermistor probe inserted into the right femoral vein and was maintained at 37 ± 1°C with heating lamps, pads, and heated humidified inspired O₂.

Arterial pressure (via femoral artery) and central venous pressure (via an external jugular vein) were measured. Pulmonary arterial and pulmonary arterial occlusion pressures (via femoral vein) were measured with a flow-directed Swan-Ganz catheter (American Edwards 93A-131H-7F). Pressures were measured continuously on an eight-channel Grass polygraph (model 7WC16PA, serial no. 791W3). The transducers (Statham model P23BB and Gould-Statham model P23Db) were zeroed at the midcardiac level and calibrated to millimeters of mercury or centimeters of water as appropriate. Thermodilution cardiac outputs (Edwards cardiac output computer model 9510-A) were measured in triplicate using an injection of 5 mL of ice-cold 5% dextrose in water.

In the atelectasis group only, intrapleural pressure was measured directly (9). After the 100% O₂ measurement was made, the left thorax was shaved and the fourth or fifth intercostal space was located in the area between the midclavicular and anterior axillary line. A 5-ml, saline-filled syringe was attached through a three-way stopcock to a plastic 15-gauge, 6-cm over-the-needle catheter (Jelco Laboratories, model 4001). The needle bevel was held parallel to the skin and directed cephalad over the superior aspect of the rib. The point was advanced slowly while pressure was maintained on the syringe barrel.

When resistance to injection ceased with a change in the volume of saline in the syringe, the intrapleural space was considered to have been entered. The plastic cannula was slipped over the needle and attached to a saline-filled pressure transducer.

In the dogs with one-lung atelectasis, after the closed chest portion of the study was completed, the chest was opened to ambient pressure to obtain a reference point for an intrapleural pressure of zero. After the chest was opened to atmosphere, the left lung was found to be completely collapsed and atelectatic in all dogs and the intrapleural location of the pleural catheter was confirmed.

Study Design

The study was divided into two groups of six dogs each. In both groups, the right lung was ventilated continuously with 100% O₂ throughout the study. The left lung was either ventilated with 100% O₂ (hyperoxia) and subsequently allowed to undergo resorption atelectasis (atelectasis) or ventilated immediately with a hypoxic gas mixture containing 4% O₂, 3–4% CO₂, balance N₂ (hypoxia). In the atelectasis group (group I), pleural pressure was measured, and in addition to three phases of 0, 15, and 90 minutes of left lung atelectasis, a fourth phase with median sternotomy was performed to obtain a zero reference point for the pleural pressure measurements. The hypoxia group (group II) differed from the atelectasis group in that no pleural pressure was measured and the study consisted of only the three phases where measurements were made at 0, 15, and 90 minutes of left lung hypoxia. Measurements were made after 10–15 minutes when stable responses of pulmonary blood flow and pulmonary perfusion pressure were noted.

Measurements

At each phase, the following measurements were made: peak and mean airway (Paw), pulmonary arterial (PAP) and systemic arterial (SAP), central venous (CVP), and pulmonary artery occlusion (PAOP) pressure; total cardiac output (CO) by thermodilution in triplicate; body temperature (temp); inspired, end-tidal, and mixed expired O₂ tensions (IL 407 oxygen analyzer) and CO₂ tensions (Godart capnograph). Arterial and mixed venous blood gas samples were collected to determine pH, Po₂, Pco₂ (Instrumentation Laboratories model 113 ultramicro blood gas analyzer), and hemoglobin (Hb) concentration (Radiometer Hemoximeter model OSM2). Right and left tidal volume (TV), respiratory rate (RR), and minute ventilation (\dot{V}_E) were recorded.

Calculations

From the recorded data, blood flow and pulmonary vascular resistance were calculated. Pulmonary per-

fusion pressure (PPP) in mm Hg was calculated as mean PAP minus mean PAOP. The total pulmonary vascular resistances in dynes·cm⁻⁵·sec were calculated from the perfusion pressure in millimeters of mercury ($\times 80$) divided by the cardiac output in liters per minute.

With 100% O₂ ventilation, alveolar oxygen tension (Pa_{O₂}) for the lung was calculated from the barometric pressure minus the saturated water vapor pressure minus Pa_{CO₂}. During hypoxic ventilation, the addition of CO₂ to the inspired gas was sufficient to introduce errors (2). Therefore, left lung Pa_{O₂} was calculated as the mean of the measured mixed-expired P_{O₂} and the mixed venous oxygen tension (P \bar{V} _{O₂}). End-capillary oxygen tension was assumed to be equal to the calculated alveolar oxygen tension. The blood oxygen contents (Co₂) of end-capillary, arterial, and mixed venous blood were then calculated from

$$\text{Co}_2 = (1.34 \times \text{Hb} \times \% \text{ sat}) + (\text{Po}_2 \times 0.0031),$$

where Co₂ = blood oxygen content in ml O₂/dL blood, 1.34 = O₂ capacity of hemoglobin in ml/g Hb (10), Hb = hemoglobin in g/dL blood, % sat = percent saturation, Po₂ = oxygen tension in mm Hg, and 0.0031 = dissolved O₂ in mL O₂·mm Hg⁻¹·dL⁻¹ blood. Percent saturation (% sat), corrected for pH and temperature, was calculated from a nomogram for canine hemoglobin (11).

Percent venous admixture (%VA) was calculated (12). Calculation of venous admixture during left lung hypoxia and atelectasis was based on a variation of the traditional shunt equation that allowed for the difference between alveolar oxygen tension in the hypoxic and hyperoxic lung (2,3). This equation assumed 1) that the total anatomic shunt flow (\dot{Q}_s/\dot{Q}_t) measured during 100% O₂ ventilation remained unchanged during hypoxic ventilation for corresponding experimental conditions and, 2) that the apportionment of anatomic shunt flow whether to the right lung or the left lung also remained unchanged during hypoxic ventilation. The errors associated with these assumptions regarding the anatomic shunt flow during 100% O₂ ventilation were small compared to the variations in left lung flow during the experimental conditions.

Statistics

The data were analyzed by a one-way within-subjects analysis of mixed design with Neuman-Keuls test for specific differences. The data from the present study were compared to data from other studies from our

Table 1. General Hemodynamic and Blood Gas Values (Mean \pm SE)

	Atelectasis	Hypoxia
pHa	7.394 \pm 0.009	7.424 \pm 0.019
Pa _{CO₂} (mm Hg)	38.7 \pm 2.0	42.0 \pm 3.8
Temp (°C)	37.2 \pm 0.2	37.8 \pm 0.2
Hb (g/dL)	13.1 \pm 0.5	12.8 \pm 0.8
HR (beats/min)	188 \pm 9	173 \pm 8
SAP (mm Hg)	43 \pm 6	136 \pm 10
SVR (dyn·cm ⁻⁵ ·sec)	3082 \pm 281	3764 \pm 561
CO (L/min)	3.78 \pm 0.34	3.08 \pm 0.30
CVP (mm Hg)	3.0 \pm 1.2	2.2 \pm 0.5
Paw _R (cm H ₂ O)	8.3 \pm 0.5	8.3 \pm 0.7
Paw _L (cm H ₂ O)	7.7 \pm 0.3	9.3 \pm 0.3

Abbreviations: pHa, arterial pH; Pa_{CO₂}, arterial P_{CO₂}; Temp, body temperature; Hb, hemoglobin; HR, heart rate; SAP, mean systemic arterial pressure; SVR, systemic vascular resistance; CO, cardiac output; CVP, central venous pressure; Paw_R, mean airway pressure of the right lung; Paw_L, mean airway pressure of the left lung.

laboratory using a comparison of means of two independent samples. A value of $P < 0.05$ was considered indicative of statistical significance. Results are expressed as mean \pm SE.

Results

Since the general baseline mean experimental conditions during measurements of central venous pressure (CVP), heart rate (HR), arterial pH (pHa), arterial carbon dioxide tension (Pa_{CO₂}), temperature (temp), cardiac output (CO), systemic vascular resistance (SVR), and mean right and left airway pressures (Paw_R and Paw_L) remained essentially constant in all individual phases of the study, only the control measurements made during 100% O₂ ventilation are presented (Table 1).

Hemoglobin decreased from 12.1 \pm 0.6 g/dL at 15 minutes of hypoxic ventilation to 10.9 \pm 0.5 g/dL at 90 minutes. This decrease in hemoglobin with blood sampling did not occur in dogs subjected to atelectasis because they were transfused with homologous blood between the 15- and 90-minute measurement periods; this was done in anticipation of blood loss occurring with median sternotomy and thoracotomy.

Mean systemic blood pressure decreased significantly only in the dogs subjected to left lung atelectasis between the 90-minute closed chest measurement (144 \pm 5 mm Hg) and after median sternotomy (130 \pm 7 mm Hg).

Intrapleural pressure measurements were made only in dogs subjected to left lung atelectasis. During 100% O₂ ventilation with the chest closed, the mean intrapleural pressure of the hemithorax was 5.4 \pm 0.7 cm H₂O and decreased significantly to -3.8 \pm 1.7 cm

Table 2. Effect of Atelectasis and Hypoxia on Various Hemodynamic and Blood Gas Parameters (Mean \pm SE)

	100% O ₂	Atelectasis			100% O ₂	Hypoxia	
		15 min	90 min	Open		15 min	90 min
Pa _{O₂} (mm Hg)	547	185*	169*	267*	544	170*	233*
	18	38	37	33	24	37	33
Pv̄ _{O₂} (mm Hg)	67	53*	50*	51*	53	43	45
	5	2	2	2	3	3	3
PPP (mm Hg)	8	18*	17*	13*	8	12*	14*
	1	0	1	2	1	5	1
PVR _t (dynes·cm ⁻⁵ ·sec)	167	406*	377*	314*	242	311	334
	29	51	21	40	50	36	25
PVR _L (dynes·cm ⁻⁵ ·sec)	387	1576*	2059*	1507	543	1757*	2134*
	63	344	283	139	114	221	364
%VA	10.3	33.2*	34.6*	25.4*,†	9.2	29.9	25.1*
	2.0	2.6	3.8	2.3	1.6	4.2	2.9
Ppl (cm H ₂ O)	5.4	-3.8*	-4.2*	0*,†			
	0.7	1.7	0.8				

*Significantly different from 100% O₂ ventilation ($P < 0.05$).†Significantly different from 100% O₂, 15 minutes, 90 minutes ($P < 0.05$).Abbreviations: Pa_{O₂}, arterial oxygen tension; Pv̄_{O₂}, mixed venous oxygen tension; PPP, pulmonary perfusion pressure; PVR_t, total pulmonary vascular resistance; PVR_L, pulmonary vascular resistance of the left lung; %VA, venous admixture; Ppl, mean intrapleural pressure of the left hemithorax.

H₂O by 15 minutes and -4.2 ± 0.8 cm H₂O by 90 minutes; all these values were referenced to zero with the chest open.

The venous admixture (%VA) increased significantly between hyperoxia ($10.3 \pm 2.0\%$) and 15 and 90 minutes of atelectasis ($33.2 \pm 2.6\%$ and $34.6 \pm 3.8\%$). However, after the chest wall was open with the left lung still atelectatic, the %VA decreased significantly to $25.4 \pm 2.3\%$. The %VA increased significantly between the pre-hypoxia control period ($9.2 \pm 1.6\%$) and 15 and 90 minutes of left lung hypoxia ($29.9 \pm 4.2\%$ and $25.1 \pm 2.9\%$).

The Pa_{O₂} decreased significantly between 100% O₂ ventilation and left lung atelectasis or left lung hypoxia at 15 and 90 minutes (Table 2). However, mean Pa_{O₂} values at 15 and 90 minutes of atelectasis with the chest closed did not differ significantly from atelectasis with the chest open. The Pv̄_{O₂} decreased significantly between the 100% O₂ and left lung atelectasis but not between 100% O₂ and hypoxia. Pulmonary perfusion pressure (PPP) increased significantly between hyperoxia and left lung atelectasis or left lung hypoxia at 15 and 90 minutes. While total pulmonary vascular resistance (PVR_t) increased significantly from 100% O₂ ventilation in the dogs exposed to atelectasis, the changes were not significant in dogs exposed to hypoxia. The pulmonary vascular resistance of the left lung (PVR_L) increased significantly between 100% O₂ ventilation and left lung atelectasis or left lung hypoxia. However, between atelectasis at 90 minutes with the chest closed and atelectasis with the chest open, neither PPP, PVR_t nor PVR_L decreased significantly.

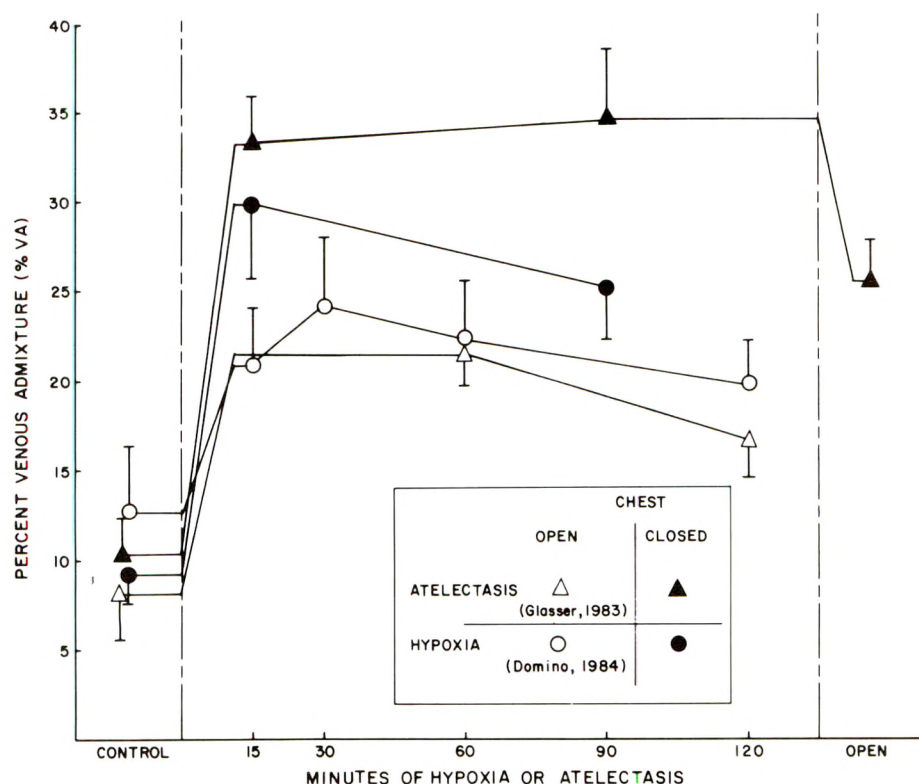
Discussion

The dual responses of hypoxic pulmonary vasoconstriction are an increase in pulmonary artery pressure and a change in pulmonary blood flow. This study demonstrated in dogs with an intact thorax that there was a regional increase in pulmonary vascular resistance of the left lung and that due to the presence of HPV the increase in %VA during left lung atelectasis or hypoxia was less than expected. However, during left lung atelectasis, after the chest was opened, with the concomitant increase in pleural pressure, %VA decreased even further, which indicated an improved HPV response.

These results from the present study during atelectasis and hypoxia in closed chest dogs were compared with data from previously published studies in a similar dog model of time course of the HPV response with atelectasis (2) and hypoxia (3) in open chest dogs (Fig. 1). During atelectasis, %VA with the chest closed at 90 minutes ($34.6 \pm 3.8\%$) was significantly greater than %VA at 60 minutes ($21.5 \pm 1.8\%$) and at 120 minutes ($16.7 \pm 2.1\%$) with the chest open. The HPV response was diminished in the closed chest dogs; it is possible that the negative intrapleural pressure pulled open the vessels in the closed chest dogs compared to the open chest dogs. However, with left lung atelectasis, %VA with the chest open in the present study ($25.4 \pm 2.3\%$) was also significantly greater than %VA with the chest open at 120 minutes ($16.7 \pm 2.1\%$) (2).

The fact that %VA values were not equal between the present study and the previous study during the

Figure 1. The effect of left lung atelectasis and hypoxia on percent venous admixture in open and closed chest dogs. Present study: (\blacktriangle) closed chest atelectasis, (\bullet) closed chest hypoxia. Previously reported studies: (\triangle) open chest atelectasis (2), (\circ) open chest hypoxia (3).



atelectasis open chest phases may be attributed to inhibition of HPV by the surgical trauma of sternotomy that immediately preceded the final measurement in the present study (13-16). This may also account for the fact that PPP and PVR_t decreased slightly, although not significantly, when the chest was open to atmosphere and it might have been expected that the loss of negative intrapleural pressure would cause the vessels to constrict more.

In contrast, during hypoxia, %VA with the chest closed at 90 minutes ($25.1 \pm 2.9\%$) was not significantly different from %VA with the chest open at 60 minutes ($23.3 \pm 3.2\%$) and at 120 minutes ($19.7 \pm 2.5\%$) (3), nor were %VA values different at 15 minutes for the closed versus open chest, respectively ($29.9 \pm 4.2\%$ versus $20.8 \pm 3.3\%$).

That %VA at 90 minutes of closed chest atelectasis (34.6%) was not significantly different from closed chest hypoxia (25.1%) may have been due to intergroup variability. The %VA at 90-minutes closed chest atelectasis (34.6%) was significantly greater than %VA at 120-minutes open chest atelectasis (16.7%), whereas %VA at 90-minutes closed chest hypoxia (25.1%) was not significantly different from %VA at 90-minutes open chest atelectasis (16.7%); perhaps with more animals in each group the difference between atelectasis and hypoxia might have reached statistical significance (Fig. 1).

Although the overall $\bar{P}\dot{V}_{O_2}$ appears to be lower in the hypoxia group, this difference was not statistically significant. The variability may have been due to the small but not statistically significant differences in cardiac output and hemoglobin. In the hypoxia group, the $Fi_{O_2} = 0.04$ was chosen so that PA_{O_2} would approximate $\bar{P}\dot{V}_{O_2}$.

In open chest dogs when the lung is either hypoventilated (and hypoxic) or partially atelectatic so that lung volumes are below FRC, HPV determines PVR rather than mechanical factors (17); after administration of the vasodilator SNP, which completely inhibited HPV, the remaining resistance was similar in both atelectatic or hypoxic ventilated lung. However, in closed chest dogs, intrapleural pressure may contribute to decreasing HPV.

This study examined the effects of open versus closed chest conditions on the effectiveness of HPV for diverting blood flow away from atelectatic lung compared to hypoxic lung. The more lung that is atelectatic, the more negative the intrapleural pressure becomes. One effect of this pressure is to delay collapse of the lung. A second effect of the negative intrapleural pressure is to increase the transmural pressure across the blood vessel walls with the expectation that the vessels will be pulled open and that this distention will reduce hypoxic pulmonary vasoconstriction. These concepts are supported by the in

vitro study by Quebbeman and Dawson (8). They subjected an isolated cat lung lobe to different degrees of inflation by changing pleural pressure. With the lung atelectatic and the $\dot{P}\bar{V}_{O_2}$ maintained at 33 mm Hg, decreasing the pleural pressure decreased the PPP so that eventually HPV was abolished.

Pirlo et al. (1) examined left lower lobe (LLL) blood flow with N_2 ventilation versus atelectasis in open-versus closed chest dogs with positive pressure versus spontaneous ventilation. No differences among these conditions were found. However, 1) their measurements were made after artificially converting an open chest dog to a closed chest preparation and after removing any residual pleural air through a chest tube by intermittent suction; 2) pleural pressure did not change significantly during LLL absorption atelectasis; and 3) the left lower lobe is only a small portion of the lung and may not have generated sufficiently negative intrapleural pressure.

Ordinarily the intrapleural pressure at end-expiration is approximately 5 cm H_2O below atmospheric pressure, or slightly subatmospheric. Intrapleural pressure is less negative at the bottom than at the top of the lung. However, differences in pleural pressure may be related to the cause of atelectasis whether it results from pneumothorax or hemothorax or from sources of compression such as tumors or surgical retraction. Pneumothorax is defined as the presence of gas in the pleural space. In the example of a bronchopleural fistula, end-expiratory pressure equals alveolar pressure and therefore equals atmospheric pressure or 0 cm H_2O . In tension pneumothorax, high pleural pressures (10–25 cm H_2O) produce atelectasis, displacement of the mediastinum, and impedance of venous return. In closed pneumothorax, pressure in the pleural space increases slightly but usually remains subatmospheric. Normally this gas is removed slowly by the capillary and venous circulation, and as the lung reexpands the intrapleural pressure remains the same. Pleural adhesions sometimes prevent the reexpansion of a lung after pneumothorax. The continued absorption of intrapleural gas then produces markedly subatmospheric pleural pressures, which favor the formation and accumulation of a transudate (ex vacuo effusion).

The most common causes for pleural effusion are neoplasms, congestive heart failure, and infection. Large exudative pleural effusions compressing the lung may occur 48–72 hours after abdominal operations, most often after splenectomy or surgery for intestinal obstruction, and in patients with postoperative atelectasis (18).

There are several other factors that affect intrapleural pressure (19). With age the lung loses some of

its elastic recoil, and intrapleural pressure therefore becomes less negative. Positive airway pressure will increase intrapleural pressure; the extent of airway pressure transmission to the intrapleural space will depend on airway resistance, lung compliance, and thoracic wall compliance and may vary greatly among patients.

In summary, HPV diverted blood flow away from atelectatic or hypoxic lung in the closed chest dogs. At 90 minutes, %VA was greater during atelectasis than during hypoxia. Due to the negative intrapleural pressure generated during left lung resorption atelectasis, HPV was less effective during atelectasis than during hypoxia.

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Sixty-Two Years Ago In

Anesthesia & Analgesia

R. M. Waters: Advantages and technique of carbon dioxide filtration with inhalation anesthesia. Current Researchs in Anesthesia & Analgesia 1926;5:160-2.

The introduction of clinically practical methods for effectively removing carbon dioxide from air represents one of the most important advances in the history of clinical anesthesia. Without CO₂ absorption, anesthesia machines as we know them today would be impossible. Previous articles by D. E. Jackson (*Lab Clin Med* 1916;2:94) and by Waters himself (*Curr Res Anesth Analg* 1924;3:20) dealt with the principles upon which carbon dioxide absorption is based. This article by Waters, at the time an anesthetist in Kansas City, Missouri, describes the clinical use of a canister filled with soda lime for absorption of carbon dioxide. Patients exhaled through the canister (placed as near as possible to the patient's airway) into a reservoir bag and inhaled the next breath, free of CO₂, from the reservoir bag, passing again through the canister (i.e., a to-and-fro canister). This revolutionary innovation meant that inhalation anesthesia could be given without dilution by room air; nitrous oxide, for example, could be more effectively administered. High concentrations of oxygen could be given. Heat was conserved. Pollution of the operating room air was avoided (pollution was a problem even in 1926). The principle of CO₂ absorption using the to-and-fro canister was eventually supplanted by soda lime canisters for circle systems. The to-and-fro canister, however, set the stage for the subsequent introduction of cyclopropane and, even later, halogenated inhalation anesthetics that could not be given using open techniques. The stage was also set for initiation of assisted and, finally, controlled respiration, the need for which did not become apparent for another 25 years.

The Increase in Urinary Alanine Aminopeptidase Excretion Associated with Enflurane Anesthesia Is Increased Further by Aminoglycosides

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MOTUZ DJ, WATSON WA, BARLOW JC, VELASQUEZ NV, SCHENTAG JJ. The increase in urinary alanine aminopeptidase excretion associated with enflurane anesthesia is increased further by aminoglycosides. *Anesth Analg* 1988;67:770-4.

Urinary excretion of alanine aminopeptidase (AAP) is an extremely sensitive indicator of drug-induced renal tubular damage. The urinary excretion of AAP was determined in patients after enflurane anesthesia with or without concurrent aminoglycoside administration to determine if enflurane enhances the nephrotoxic potential of aminoglycosides. Twenty-two patients with normal renal function were studied. Ten received enflurane alone, eight received enflurane plus gentamicin or tobramycin, and four patients who underwent nitrous oxide and narcotic anesthesia were the control group. Preoperative values ranged from 1010 to

2461 $\mu\text{U}/24$ hour. Urinary AAP excretion increased significantly in both enflurane groups 2 days postoperatively ($P < 0.025$). Patients who received both enflurane and aminoglycosides had significantly greater urinary AAP excretion on postoperative day 2 than did patients given enflurane alone: $21,342 \pm 4074$ $\mu\text{U}/24$ hour and 6336 ± 1496 $\mu\text{U}/24$ hour, respectively (mean \pm SEM, $P < 0.005$). There was no change in AAP excretion in the control group compared to baseline; on day 3 AAP was 1412 ± 710 $\mu\text{U}/24$ hour. No changes in blood urea nitrogen or serum creatinine levels were observed. These data suggest that enflurane increases the renal tubular effects of aminoglycosides, possibly increasing the risk of aminoglycoside renal toxicity.

ANESTHETICS, VOLATILE—enflurane. KIDNEY—tubular function. ANTIBIOTICS—aminoglycosides.

Increased urinary excretion of renal tubular enzymes is a sensitive indicator of drug-induced renal tubular injury. Enzymuria generally occurs before overt nephrotoxicity, and enzymuria of major proportions invariably precedes the onset of acute renal failure (1). Alanine aminopeptidase (AAP) is an enzyme found in the brush border membrane of the proximal renal tubule (2). When excreted in urine, AAP is

easily measured and serves as a sensitive measure of proximal renal tubule cellular damage (3).

Previous evaluations of the nephrotoxic potential of the fluorinated inhalation anesthetics have relied on clinical indicators of nephrotoxicity such as blood urea nitrogen (BUN), serum creatinine, urine composition and concentrating ability, and measurements of serum and urine inorganic fluoride levels (4,5). Using these parameters, Barr et al. (6) demonstrated that methoxyflurane nephrotoxicity was potentiated by the concurrent administration of gentamicin. Similar studies of enflurane did not demonstrate clinical evidence of nephrotoxicity, either alone or combined with gentamicin (7). This suggests that either no renal tubular injury occurred or that the renal insult was undetectable using these measures. Discrimination between these two possibilities is important if a high-risk patient population exists that might react adversely to the combination of two relatively mild insults. Rather than study high-risk patients to ad-

Preliminary results were presented at the American Society of Anesthesiologists 1986 Annual Meeting in Las Vegas, NV.

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dress this question, we used a more sensitive index of renal dysfunction to allow the study of low-risk patients, namely, urine AAP concentrations as an indicator of subclinical renal insult in patients. The effect of enflurane and concurrent enflurane-aminoglycoside therapy on urinary AAP excretion was evaluated to determine if enflurane enhances the nephrotoxic potential of aminoglycosides.

Methods

After approval by the Millard Fillmore Hospital Human Research Committee, patients with normal renal function scheduled to undergo elective surgery were enrolled in the study after providing written informed consent. Patients were excluded from study if they were undergoing surgery involving the kidneys or coronary artery bypass. They were classified into three groups: group I received enflurane alone and group II received an aminoglycoside before enflurane. Patients anesthetized with nitrous oxide and narcotics were used as the control group. Aminoglycoside administration was determined by the patient's surgeon, who was not otherwise involved in the study. Either gentamicin or tobramycin was used.

All patients received preoperative medication consisting of diazepam, glycopyrrolate, and dihydromorphone. Induction was achieved with thiopental (5 mg/kg) followed by succinylcholine (1 mg/kg) to facilitate intubation. A nondepolarizing muscle relaxant (pancuronium, vecuronium, or atracrium) was added to maintain surgical muscle relaxation. Narcotics were administered as required along with nitrous oxide:oxygen in a 70:30% mixture.

Serum uric acid, creatinine, and blood urea nitrogen (BUN) were measured preoperatively and 24 and 48 hours postoperatively. Postoperative 24-hour urine output and fluid administration were recorded for the 2-day period after surgery. Urinary AAP activity was measured in 10-ml urine samples collected preoperatively and 24 and 48 hours postoperatively. All samples were collected in the morning. Laboratory studies performed between the end of the study period and discharge were recorded to determine if alterations in renal function were observed after the study period.

Urine AAP activity was determined using the method described by Mondorf et al. (3). The assay is based on the conversion of alanine-4-nitroanilide in the presence of AAP to alanine and 4-nitroaniline. The amount of product formed over a 5-minute period is determined by the change in absorbance at 405 nm. The activity ($\mu\text{U/ml}$) is calculated using the formula

Table 1. Demographics of the Study Patients

	Enflurane alone	Enflurane with Aminoglycosides	Control
Number of patients	10	8	4
Male/female	5/5	5/3	2/2
Age (years)	61 \pm 5.2	63 \pm 9.8	43 \pm 8
Weight (kg)	74 \pm 3.79	67 \pm 9.8	82 \pm 3
ASA status			
I	1	0	2
II	5	4	2
III	4	4	0
Surgical procedures	Abdominal, neurosurgery, skin grafting, vascular	Abdominal	Orthopedic
Duration of anesthesia (minutes)	160 \pm 24	155 \pm 19	191 \pm 27

*Values are given as mean \pm SEM.

$$\text{activity} = \frac{\text{VT}}{(\text{E}_{405})(\text{Vs})(1)} \times \frac{\text{A}}{\text{min}}$$

where VT is the total volume of the assay solution, Vs is the urine sample volume, A is absorbance change per minute, 1 is the spectrophotometer light path (cm), and E_{405} is the extinction coefficient for 4-nitroaniline at 405 nm. The AAP activity per milliliter of urine is multiplied by the 24-hour urine volume to calculate microunits of enzyme activity excreted per 24 hours.

Repeated measures analysis of variance (ANOVA) was used to compare the change in laboratory values, urine output, fluid administration, and urinary AAP activities over the 3-day study period and to compare the treatment groups. Data are presented as the mean \pm SEM. Tukey's method of post-hoc multiple comparisons was used to compare pairs of means after ANOVA showed significant effects. The criterion of statistical significance was $P < 0.05$ for all comparisons.

Results

Twenty-two patients completed the study. The demographics, clinical status, and surgical procedures of the two treatment groups were similar (Table 1). The control group was different only in that all patients underwent orthopedic surgery. The preoperative renal function in each group of patients studied was similar. Baseline urinary AAP values were not different than those of healthy volunteers. Eight of the 22 patients received either gentamicin ($n = 4$) or tobramycin ($n = 4$) (Table 2). The remaining patients

Table 2. Aminoglycoside Dosing Regimen*

	Gentamicin	Tobramycin
Number of patients	4	4
Daily administered dose (mg/kg)	3.4 ± 0.20	3.0 ± 0.06
Number treated before enflurane	0	1
Number started perioperatively	4	4
Duration of therapy (days)	2.4 ± 0.4	8.0 ± 1.35

*Values are given as mean ± SEM.

received nonnephrotoxic antibiotics in addition to their anesthesia. The enflurane dose was similar in the two treatment groups. In group I, the dose ranged from 0.5 to 1.0% for an average of 106 minutes; and group II received 0.75 to 1.25% enflurane for an average of 154 minutes.

Postoperative serum uric acid, creatinine, and BUN were not different from preoperative values (Table 3). Postoperative urinary AAP activity was higher than the preoperative values in both enflurane groups. This was statistically significant 2 days postoperatively (Fig. 1). Urinary AAP levels 2 days after surgery were also significantly higher in group II (enflurane and aminoglycosides) than in the group that received enflurane alone. There were no postoperative changes in AAP excretion in the control group; the excretion averaged $1288 \pm 458 \mu\text{U}/24$ hour preoperatively, $1745 \pm 268 \mu\text{U}/24$ hour on postoperative day 1 and $1412 \pm 710 \mu\text{U}/24$ hour on postoperative day 3.

Urine output and fluid administration were similar in both enflurane groups on the first postoperative day. During the second postoperative day, urine output was significantly greater in group II (3433 ml) than in group I (2306 ml). Fluid intake was also significantly greater in group II (3567 ml) than in group I (2284 ml).

Discussion

AAP excretion in the urine is a sensitive and specific indicator of renal tubular damage. We used this enzyme to determine if previous studies of enflurane nephrotoxicity, using less sensitive indicators of renal tubular function such as creatinine and BUN, may have been unable to detect subclinical renal damage.

Urinary AAP activity increased significantly above preoperative values in enflurane-treated patients 48 hours after surgery. The control group did not have any increase in AAP excretion on the third postoperative day, suggesting that enflurane causes an increase in urinary AAP excretion. In spite of these renal tubular enzyme data, enflurane appears capable

of producing clinically significant nephrotoxicity only under unusual or extreme conditions. Studies in healthy volunteers have shown that prolonged exposure to high concentrations of enflurane is nephrotoxic, and there are isolated reports of renal failure in patients after enflurane anesthesia (5,8,9). Like methoxyflurane, enflurane metabolism results in fluoride ion release, but the amount of fluoride ion produced after typical anesthetic doses is too small to cause clinical signs of renal failure (10).

Aminoglycosides produce dose-related increases in urinary AAP after administration to healthy adults. Mean urine AAP excretion achieves peak values of approximately $6500 \mu\text{U}/\text{day}$ an average of 3 to 4 days after drug administration (3). Gentamicin, methoxyflurane, and fluoride ion all damage the proximal renal tubule, and the toxicity is characterized by vasopressin-resistant polyuria (5,6,11,12). Therefore, one would expect aminoglycosides and fluorinated anesthetics such as enflurane to potentiate each other's nephrotoxicity. Our finding that postoperative urinary AAP levels increased to higher levels in patients treated with enflurane and aminoglycosides compared to patients who received enflurane alone demonstrates additional subclinical renal tubular damage in patients receiving the combination of enflurane and an aminoglycoside. Compared to previous urine enzyme measurements in patients receiving aminoglycosides alone, the patients who received enflurane and aminoglycosides in this trial appeared to develop elevation of urine AAP more rapidly, with high concentrations seen the second postoperative day. Previous studies from this laboratory have shown that urinary enzyme concentrations peak between 4 and 5 days after aminoglycoside therapy is initiated (13).

During the postoperative period, none of our patients developed evidence of renal failure (increased levels of serum uric acid, creatinine, or BUN). Glomerular filtration rate must decrease by 30 to 50% before serum creatinine increases. Schentag et al. (13) have shown that the increase in serum creatinine lags 5 to 7 days behind enzymuria during aminoglycoside toxicity. If urinary AAP had not been measured, we would have concluded that there were no renal tubular effects in either enflurane group.

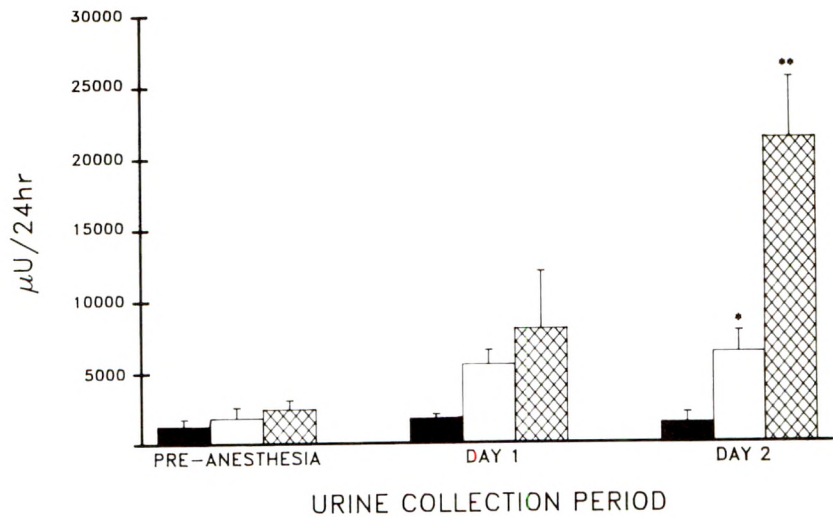
In summary, we observed an increase in urinary AAP without clinical evidence of renal insufficiency in patients with normal renal function receiving enflurane alone or enflurane plus an aminoglycoside. Clinical nephrotoxicity may not always be apparent if the amount of damage is too slight to overcome the large reserve of the kidney. The measurement of AAP is a useful, early, and highly sensitive indicator of

Table 3. Systemic Indicators of Renal Function*

	Serum creatinine (mg%)	Serum uric acid (mg%)	Blood urea nitrogen (mg%)
I. Enflurane			
Preoperative	0.96 ± 0.03	4.90 ± 0.51	13.90 ± 1.05
Postoperative			
Day 1	0.88 ± 0.07	4.65 ± 0.54	10.80 ± 0.91
Day 2	0.87 ± 0.05	4.11 ± 0.48	10.44 ± 1.07
End of hospital stay	0.93 ± 0.07	—	14.33 ± 0.80
II. Enflurane and Aminoglycoside			
Preoperative	1.02 ± 0.11	4.60 ± 0.53	14.60 ± 2.61
Postoperative			
Day 1	1.11 ± 0.14	3.85 ± 0.50	12.12 ± 0.86
Day 2	1.11 ± 0.11	3.45 ± 0.50	9.25 ± 4.24
End of hospital stay	0.86 ± 0.15	—	16.00 ± 5.65

*Values are given as mean ± SEM.

Figure 1. Urinary excretion of AAP (μU/24 hours). The open bars represent patients given enflurane alone (group I), the cross-hatched bars represent patients given enflurane and aminoglycosides (group II), and the solid bars represent control patients. The asterisk indicates $P < 0.05$ when compared to pre-enflurane values for treatment group I. The double asterisks indicate $P < 0.025$ when compared to preoperative baseline values in group II and $P < 0.005$ compared with group I on day 2. The control group value for the third postoperative day is shown graphically on day 2.



renal tubular damage, and its elevation indicates that high-risk patients may demonstrate overt renal tubular damage when enflurane is combined with aminoglycosides. Patients with abnormal preoperative renal function who require both enflurane and aminoglycosides need to be studied to determine if the expected increase in AAP excretion is a predictor of clinically significant renal damage.

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Duration of Action of Neostigmine and Pyridostigmine in the Elderly

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YOUNG WL, MATTEO RS, ORNSTEIN E. Duration of action of neostigmine and pyridostigmine in the elderly. *Anesth Analg* 1988;67:775-8.

This study was undertaken to assess differences between young and elderly patients with respect to the duration of antagonism of metocurine neuromuscular blockade by neostigmine (NEO) or pyridostigmine (PYR). Patients were given either NEO (seven elderly and ten young) or PYR (seven elderly and eight young) and received nitrous oxide in oxygen (60:40) and 1 MAC halothane. Neuromuscular transmission was assessed by using evoked compound electromyography. Metocurine 0.1 mg/kg was given, followed by a continuous infusion to achieve 90% reduction in baseline single twitch height. After at least 30 minutes, either NEO (0.07 mg/kg) or PYR (0.14 mg/kg) and atropine (0.02 mg/kg) were given IV. After injection of NEO or

PYR, the duration of maximal response (DOMR) was recorded. Mean (\pm SE) ages were 38 ± 5 and 68 ± 2 years in the two groups of patients receiving PYR. In the elderly, PYR significantly prolonged DOMR compared to younger patients (35.3 ± 8.2 vs 14.4 ± 4.2 minutes, respectively). The mean ages in the two groups of patients receiving NEO were 41.5 ± 4 and 72 ± 2 years. The elderly group demonstrated a significant increase in the DOMR compared to younger patients (32 ± 10 vs 11 ± 2 minutes, respectively). It is concluded that, compared to younger patients, the duration of action of NEO and PYR in the aged patient is prolonged.

NEUROMUSCULAR RELAXANTS—metocurine. ANTAGONISTS, NEUROMUSCULAR RELAXANTS—neostigmine, pyridostigmine. AGE FACTORS—duration of action of relaxant antagonists.

A significant proportion of patients coming under anesthesiologists' care fall under the classification of "elderly." As reviewed by Miller (1), over 11% of the population is over age 65, a figure that is probably increasing; over half of these elderly will require surgery before they die. Del Guercio and Cohn (2) estimate that more than 100,000 patients in the United States alone over the age of 65 will die each year during or after anesthesia and surgery. Studies of anesthetic management techniques are thus important to reduce the increased morbidity and mortality that care of these patients may engender. The action of most nondepolarizing muscle relaxants is prolonged in the elderly (3). Although the effect of age on the action of edrophonium has been investigated

(4,5), the influence of aging on duration of action of the other commonly used anticholinesterases used to antagonize a nondepolarizing blockade has not been investigated. This study was undertaken to assess any differences between young and elderly patients with respect to the duration of antagonism of stable neuromuscular blockade by neostigmine or pyridostigmine.

Methods

Thirty-two adult patients scheduled to undergo elective craniotomies were included in the study after obtaining institutional approval and informed consent. All patients had normal renal, hepatic, and cardiac function; none were obese; and none were receiving drug regimens (6,7) or had neurological conditions (8) known to alter the patients' response to muscle relaxants. For the purposes of this study, patients were considered to be elderly if their age was greater than 60 years. Seventeen patients were given neostigmine (seven elderly and ten young) and 15 were given pyridostigmine (seven elderly and eight

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young). The two groups were studied sequentially. Anesthesia was induced with thiopental, and tracheal intubation was facilitated with succinylcholine (Sch). Anesthesia was maintained with nitrous oxide in oxygen (60:40) and 1 MAC halothane, the inspired concentration being adjusted for age (9). Mechanical ventilation maintained moderate hypocarbia ($Paco_2$, 25–30 mm Hg) and esophageal temperatures were maintained at 34.5–36°C. Neuromuscular transmission was assessed by quantitating the height of the evoked compound electromyographic (ECEMG) response of the adductor of the thumb in response to supramaximal stimulation of the ulnar nerve at the wrist by a Grass S8 stimulator (10). The twitch responses to single stimuli of 0.2 millisecond duration delivered at a frequency of 0.1 Hz (6/minute) were recorded. After Sch administration, return of twitch height to normal was assessed by train-of-four stimulation. Immediately after the return of baseline twitch height, a bolus of 0.1 mg/kg metocurine was given, followed by a continuous infusion to metocurine to achieve 90% reduction from the baseline single twitch height. After at least 30 minutes of observation to ensure constant twitch response height, atropine (0.02 mg/kg) plus a bolus of neostigmine (0.07 mg/kg) or pyridostigmine (0.14 mg/kg) was given IV. The dose of pyridostigmine chosen was approximately one-half of the full reversal dose to enable the study to be completed within the time limits imposed by the surgical procedure.

Immediately preceding the injection of the anticholinesterase and at hourly intervals thereafter, 1-ml samples of heparinized blood were obtained from an arterial catheter for assay of metocurine concentration. Plasma from these samples was separated and frozen until analyzed by radioimmunoassay. The sensitivity of this assay is 1 ng/ml and the maximum variation is $\pm 5\%$ at all concentrations (11).

After injection of the anticholinesterase, the following times of recovery from neuromuscular blockade were recorded: start of recovery (START RESP), maximum recovery (MAX RESP), duration of maximal response (DOMR), time to 75% recovery (TT75%), time to 50% recovery (TT50%), and time to 25% recovery (TT25%). The various response times measured are depicted in Figure 1. It was not possible, especially in elderly patients, to extend the data collection period to include all variables in all patients. Comparisons between response times for elderly and younger patients in each group were made using Student's *t*-test for unpaired data (two-tailed). A *P* value of <0.05 was taken to be significant. All values are reported as mean \pm SE.

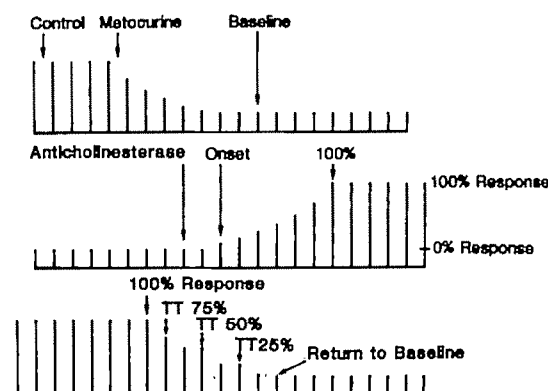


Figure 1. A schematic depiction of stimulus response heights recorded during the study.

Table 1. Pyridostigmine

	<i>n</i>	Young	<i>n</i>	Elderly
START RESP*	8	0.8 \pm 0.1†	7	1.1 \pm 0.2
MAX RESP	8	12.9 \pm 1.7	7	14.0 \pm 0.8
DOMR	7	14 \pm 4	7	35 \pm 8‡
TT75%	7	54 \pm 12	5	86 \pm 20
TT50%	7	96 \pm 19	3	123 \pm 26
TT25%	3	125 \pm 22	1	162

*Abbreviations: START RESP, start of response; MAX RESP, maximum response; DOMR, duration of maximum response; TT75%, time to 75% recovery; TT50%, time to 50% recovery; TT25%, time to 25% recovery. See Fig. 1 and text.

†Values are in minutes (mean \pm SE).

‡Significantly different from young (*P* < 0.05).

Results

Throughout the study the mean metocurine concentration in the younger patients was 0.17 ± 0.03 μ g/ml; in the elderly group it was 0.18 ± 0.04 μ g/ml. Comparing the hourly samples to the initial sample for each patient, the maximum variation in the metocurine concentrations was $<8\%$. This relatively small variation in metocurine concentration during the study confirms that the selected infusion rate for metocurine resulted in a steady state.

The mean ages in the two groups of patients given pyridostigmine were 38 ± 5 and 68 ± 2 years. The younger patients weighed significantly more than the elderly (78 ± 4 vs 64 ± 4 kg). In the elderly, pyridostigmine significantly prolonged DOMR compared to the younger patients (35.3 ± 8.2 vs 14.4 ± 4.2 minutes, respectively) (Table 1). The other onset and offset variables were not significantly different. The mean ages in the two groups of patients given neostigmine were 41.5 ± 4 and 72 ± 2 years. The weights were similar (64 ± 4 and 59 ± 5 kg). The elderly group demonstrated a significantly longer DOMR than younger patients (32 ± 10 vs 11 ± 2 minutes, respectively) (Table 2). The START RESP,

Table 2. Neostigmine

	<i>n</i>	Young	<i>n</i>	Elderly
START RESP*	10	0.5 ± 0.1†	7	0.7 ± 0.1‡
MAX RESP	10	5.7 ± 0.6	7	7.9 ± 1.5
DOMR	10	11 ± 2	7	32 ± 10‡
TT75%	9	54 ± 7	5	84 ± 12‡
TT50%	9	112 ± 16	5	183 ± 20‡
TT25%	7	129 ± 17	2	211 ± 8‡

*Abbreviations: START RESP, start of response; MAX RESP, maximum response; DOMR, duration of maximum response; TT75%, time to 75% recovery; TT50%, time to 25% recovery; TT25%, time to 25% recovery. See Fig. 1 and text.

†Values are in minutes (mean ± SE).

‡Significantly different from young ($P < 0.05$).

TT75%, TT50%, TT25%, and TF100-50% were also significantly prolonged in the elderly group.

Discussion

Our data reveal a significant increase in the duration of action of the anticholinesterase inhibitors neostigmine and pyridostigmine in the elderly. This is similar to increases in the duration of action of nondepolarizing muscle relaxants observed in older patients (3). It should be noted that we did not attempt to determine a dose-response relation for the two anticholinesterases, nor were equipotent doses of drugs used. A relatively smaller dose of pyridostigmine was chosen to allow completion of the studies within the constraints of operative time in our patient sample.

Although the pharmacodynamics of neostigmine and pyridostigmine have been investigated, these studies have not included elderly subjects (12,13). Of interest are two other reports in which no increase in the duration of edrophonium in the elderly was observed (4,5). Although studies under somewhat differing conditions make direct comparison with the present results difficult, it is nevertheless intriguing that neostigmine and pyridostigmine appear to differ from edrophonium with respect to their effects in elderly patients. As reviewed by Cronnelly et al. (14), there are a number of differences in the mechanism of action of anticholinesterase action of the three agents. These include the reversible and transient nature of edrophonium binding to the cholinesterase active site as opposed to the longer-lasting carbamylation of the esterase site by neostigmine and pyridostigmine, and there is no direct stimulation of the end-plate region with edrophonium as opposed to neostigmine. The differences in the dose-response relation of the three anticholinesterase agents support this notion (14). The pharmacokinetics of edrophonium do not differ from neostigmine and pyridostigmine in relatively

healthy adults (13,15). However, the initial volume of distribution for neostigmine appears to be larger in elderly than in young patients (16), where it is similar for edrophonium (13). The above considerations may in part explain the apparent difference in duration of action of the two classes of anticholinesterase agents. However, there are multiple changes in organ and tissue function with the aging process (5), and the explanation for the observed prolonged duration of action of the two carbamylating agents may result from as-yet unstudied pharmacodynamic phenomena.

We conclude that the duration of action of neostigmine and pyridostigmine in the elderly patient is prolonged. Because the duration of action of pancuronium, metocurine, and *d*-tubocurarine is prolonged in the elderly, it seems more appropriate to use either neostigmine or pyridostigmine to antagonize neuromuscular blockade with these relaxants rather than edrophonium.

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Clinical Reports

Twenty-Three Sequential Out-of-Hospital Halothane Anesthetics in an Infant

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Key Words: ANESTHESIA—pediatric.
ANESTHETICS, VOLATILE—halothane.

A sequence of 23 prolonged halothane anesthetics was administered over a 6-week period to a 4-month-old infant outside the confines of a hospital. Our participation allowed the successful completion of a series of unique radiation treatments, utilizing proton beam therapy, in an effort to prevent blindness in this young patient.

Case Report

The infant was a 4-month-old, 6.2-kg boy with a recurrent retinoblastoma in his left eye. At the age of 2 months, his right eye had been enucleated. The patient was otherwise in good health. Fractionated doses of proton beams were considered to be the only treatment that would eradicate the tumor while preserving residual vision. A series of 20–25 treatments was proposed, to be performed at the Harvard Cyclotron Laboratory. This unit contains basic resuscitation equipment but no other facilities for caring for anesthetized patients. Hence, all anesthetic equipment and monitors had to be transferred from our hospital.

The infant was cared for as an outpatient. The treatment sessions took place four times per week at 1:00 p.m. The child's mother would feed him milk at 6:00 a.m. and clear liquids at 8:00 a.m., after which he was kept NPO. Anesthesia was induced with rectal methohexital (10%), the dose ranging from 35 mg/kg at the beginning of the series to 55 mg/kg near its conclusion. These doses achieved mild to moderate

sedation. The infant was then placed supine on a mold designed specifically to maximize airway patency while providing access to the eye. The anesthetic depth was increased using mask ventilation with halothane, N₂O, and O₂.

A transparent surgical dressing (Steridrape) was placed over the child's face; the upper edge was adherent to the nasal bridge and extended laterally over each maxillary ridge. This created a veil under which anesthetic gases were insufflated to the spontaneously breathing infant. The affected eye was immobilized by a suction cup designed specifically for this purpose.

During the initial part of each session the path of the proton beam was adjusted according to precise specifications with several X-rays. These determinations usually required more than an hour and were followed by 5–7 minutes of actual treatment with the proton beam. The intensity of the radiation during the proton beam therapy required us to be 20 meters away from the patient in a shielded control room, monitoring the patient via television cameras. At the conclusion of treatment the anesthetic agents were discontinued; the infant was usually able to be fed within 30 minutes of awakening.

During the procedure the anesthetics were administered by insufflation through an open system. The patient's electrocardiogram, blood pressure, and pulse oximeter were carefully monitored. Capnometry was also performed by positioning the aspiration tubing of the capnograph at the outlet of the naris of the patient. A member of our team (FXV) designed a special telemetric precordial stethoscope through which amplified heart and breath sounds could be heard in the room; these sounds were then broadcast to the control room through an intercom system. Several television cameras were focused on the patient and on the monitoring equipment, allowing the patient to be observed from the control room during the actual therapy.

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At the conclusion of the 23rd anesthetic, laboratory tests were performed to exclude the possibility of hepatic, renal, or hemopoetic dysfunction. The results were: Hct 32.7%, platelets 304,000/mm³, WBC 8,600/mm³, glucose 60 mg/dL, BUN 9 mg/dL, creatinine 0.2 mg/dL, alk phosphatase 79 U/L, SGPT 21 U/L, SGOT 35 U/L, 5'-nucleotidase 4 U/L, total bilirubin 0.5 mg/dL, creatine kinase 77 U/L. These values were all within the normal range for children as measured by our laboratory.

Slight lethargy was the only behavioral change noted (by the patient's mother) during the entire time of therapy. An area of 3 cm² of temporary alopecia developed at the occiput at the site of contact with the mold. The patient's mother specifically mentioned that the appetite of the child was well maintained during the treatment interval. She detected no changes in his bowel habits. During this 6-week period the child's weight increased from 6.2 to 7.4 kg (19%); this change was due to growth and development, not fluid retention. Subsequent eye examination at 3 and 9 months after conclusion of therapy revealed complete regression of the tumor.

Discussion

Standard radiation therapy regimens require sedation for relatively short periods (1). This case was unique in that each session lasted for about 2 hours. The maintenance of adequate immobility thus required more than simple sedation. In fact, the unusual circumstances necessitated a novel anesthetic regimen.

As in most clinical situations, our primary concern was airway patency. Wishing to avoid the risk of injury and edema in the upper airway of our young patient, we decided against repeated endotracheal intubations. Further, because intrinsic eye movements had to be avoided, we could not use ketamine (2). Rectal and intramuscular methohexital were excluded as primary agents because their effects were judged insufficient in light of the length of the procedure.

Volatile anesthetics provide reliable and reversible anesthesia in the spontaneously breathing child. We chose to use halothane rather than isoflurane or enflurane because it is less irritating to the airways and thus results less frequently in coughing and laryngospasm (3,4). In the usual clinical situations these effects may jeopardize the safety of the patient for only a short time and can be easily corrected. Our circumstances, though, were much more delicate and demanding; even minor movements would have required repetition of all prior positional adjustments. Another consideration was that halothane is less of a

respiratory depressant than enflurane (5). Most important, we had much more experience with halothane anesthesia than with other volatile anesthetics for infants and felt more comfortable with its use in this isolated and difficult anesthetizing location. We foresaw the possibility that our patient might develop jaundice that might be attributed (probably unjustifiably) to the halothane (6). The findings of other authors were reassuring in this respect (7).

The insufflation anesthetic technique allowed for clinically adequate gaseous exchange and a normal hemoglobin saturation. The need to give repeated anesthetics in the same out-of-hospital location, however, led us to improve on certain techniques of monitoring. We were able to modify the precordial stethoscope to act as a telemetry unit broadcasting the heart and breath sounds to both the treatment and control rooms. This decreased the need to stay close to the patient during the repeated X-rays and the proton beam therapy. This modification also allowed everybody in the room to be "tuned in" to the cardiorespiratory pattern of the infant.

We were also concerned that our patient was to be repeatedly anesthetized without intravenous access. We considered selecting a vein in the forearm and leaving in place a cannula with a heparin lock. We could not, however, find such a convenient vein. An alternative would have been to insert a central line percutaneously or surgically. We preferred not to do this because central lines carry certain risks (8). We elected in the end not to use an IV but to optimize preanesthetic hydration by relying on the mother to maintain a strict preoperative fluid regimen. We were comforted that the patient was able to be fed less than half an hour after the end of each procedure.

Finally, we could not predict the possible effects of multiple N₂O and halothane exposures, with almost daily frequency, on hepatic, hemopoetic, immunologic, renal, and gastrointestinal function. Wark et al. (7) observed minor changes in liver function tests in children who received up to 10 anesthetics over the course of 1 year. Recent observations have suggested the possibility of hepatitis in children after repeated exposures to halothane (6). Whether these reported cases are due to a concomitant non-A, non-B hepatitis cannot be proved with our present knowledge. We were, however, ultimately gratified to see that the indexes of hepatic, renal, and hemopoetic function were essentially normal after a cumulative 27 hours of halothane N₂O anesthesia within a 6-week period.

We expected growth to be impaired or at least somewhat hindered. Interestingly, though, the feeding habits of the infant adjusted to the abnormal cycle we had created. No clinical indications of ileus or

rectal inflammation were noted. We feel that the most remarkable aspect was the infant's weight gain, an indication of normal growth during an extremely abnormal period of life.

In summary we describe here our mode of managing the daunting set of anesthetic challenges particular to this case. Conscious, and probably controversial, decisions were made using an anesthetic technique that carried with it the remote possibility of serious complications. These efforts and risks were undertaken in an attempt to preserve vision in a small infant.

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Atracurium and Hypokalemic Familial Periodic Paralysis

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Hypokalemic familial periodic paralysis (HFPP), a genetic disorder transmitted as an autosomal dominant condition, is characterized by intermittent attacks of skeletal muscle weakness precipitated by stress, cold, carbohydrate or saline load, and infection (1). Hypokalemia may be due to a disturbed membrane potential resulting from abnormal uptake of potassium by muscle cells. Anything that reduces plasma potassium appears to precipitate attacks, and measurements to prevent hypokalemia cause clinical improvement. Avoidance or sparing use of muscle relaxants during anesthesia is advised in these patients (2,3). In one report of general anesthesia in 21 patients with HFPP, postoperative muscle weakness developed only in the 3 patients given neuromuscular blockers (4). We describe the satisfactory use of atracurium in one patient with HFPP.

Case Report

A 48-yr-old man, weighing 65 kg, scheduled for elective left inguinal herniorrhaphy led a 10-yr history of HFPP that was well controlled by spironolactone and potassium supplements. Episodes of HFPP were usually precipitated by heavy work, the main manifestation being weakness of the upper and lower limbs. He had not required hospitalization since beginning therapy, and he had never had a general anesthetic.

The patient also had angina pectoris that occurred both on exertion and at rest. Coronary angiography 2 yr previously showed that he had normal coronary arteries with a dilated, poorly functioning left ventricle, suggestive of a congestive type cardiomyopathy. Echocardiography confirmed impairment of left ventricular function. The rest electrocardiograph (ECG) showed bigeminal rhythm and, on exercising, ische-

mic changes in the inferolateral chest leads. His angina was treated with 80 mg verapamil three times a day and sublingual glyceryltrinitrate.

The patient also had a hiatus hernia with reflux esophagitis being treated with ranitidine and gaviscon. There were no other noteworthy features in his history or physical examination. Routine laboratory tests were within the normal range and the plasma K^+ was 3.9 mmol/L.

The patient was premedicated with 10 mg diazepam orally and on arrival in the operating theater was calm and relaxed. Anesthesia was induced with 4 mg/kg thiopental intravenously (IV), and the trachea was intubated after administration of 0.5 mg/kg atracurium IV. Anesthesia was maintained with 66% nitrous oxide, 0.5–1.0% isoflurane, and 10mg morphine IV. A half liter of dextrose-saline was infused slowly intraoperatively. The patient's blood pressure and ECG were monitored continuously on a datascop 2100 monitor, and he remained normotensive throughout. Bigeminal rhythm present initially reverted to sinus rhythm with occasional ventricular ectopic beats during most of the procedure. There were no ECG signs of ischemia or hypokalemia. At the end of the operation, which lasted 60 min, 1.2 mg atropine IV and 2.5 mg neostigmine IV were administered. Five minutes later, the patient was awake and cooperative. Muscle power had returned sufficiently to allow him to sit partially upright, and there was no weakness of the limbs. The patient made a smooth and uneventful postoperative recovery with no episodes of HFPP. The plasma potassium was normal at all times. He was discharged 10 days later.

Discussion

The case reported here is of particular interest because of the cardiomyopathy associated with hypokalemic familial periodic paralysis and because atracurium was used. The presence of angina, coupled beats, and a known cardiomyopathy led us to opt for general anesthesia and the avoidance of spinal anes-

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thetia with its potential variable effects on the cardiovascular system. A field block, although possible for herniorrhaphy, would involve the use of quite a relatively large amount of local anesthetic with the potential for myocardial depression. The initiation of a field block might also have been more stressful than a smooth general anesthetic.

The combination of morphine, isoflurane, and atracurium produced a stable blood pressure throughout, and it was noteworthy that the initial bigemini reverted to sinus rhythm soon after induction of anesthesia. Another benefit of the technique used was the rapid and complete return of consciousness and muscle power postoperatively. We considered it important that the patient be as pain-free as possible to avoid stress, and so we chose morphine rather than a shorter-acting analgesic such as fentanyl.

Atracurium and isoflurane are suitable agents to choose where cardiac function is impaired, and the rapid hydrolysis of the former suggests that it may be an ideal relaxant for patients with HFPP. The patient in this instance might be considered to have a mild form of HFPP and, being 46 years old, might be expected to have less frequent and less severe attacks

(1). However, as most of the reported episodes of respiratory failure after anesthesia in patients with the hereditary condition he had were associated with the use of muscle relaxants (2,3), it is worth noting this one satisfactory usage of atracurium. There is no other report of the use of atracurium in patients with HFPP.

The smooth course through anesthesia, surgery, and the postoperative period was mainly due to good control of plasma potassium at all times, the avoidance of rapid carbohydrate or saline infusions, and the avoidance of stress in all its forms.

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Extent of Anesthesia and Hemodynamic Effects After Subarachnoid Administration of Bupivacaine with Epinephrine

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Key Words: ANESTHETIC TECHNIQUES—spinal.

It has been suggested that the amount of local anesthetic injected into the subarachnoid space is more important than the volume or concentration that is used in determining the extent of anesthesia (1-7). However, this conclusion was based on studies using small volumes of local anesthetic (e.g., 1-4 ml). We have used larger volumes of local anesthetic (10 ml) for subarachnoid anesthesia, with good analgesia and without complications (8). We have now evaluated the effect of using widely disparate volumes (2.5 vs 10 ml) and concentrations (0.5% vs 0.125%) of bupivacaine while maintaining a constant dose (12.5 mg) on the extent of sensory anesthesia and the resultant hemodynamic changes.

Materials and Methods

Fifty ASA category 2 or 3 patients scheduled for minor urologic procedures under spinal anesthesia were studied. The study was approved by the institutional review committee, and informed consent was obtained from all patients. All patients were premedicated with diazepam 10 mg by mouth about 90 minutes before induction of spinal anesthesia. An intravenous catheter was inserted, and infusion of glucose 2.5% in 0.45% NaCl was started at about 100 ml/hr.

Patients were randomly classified into two groups. In group A, 2.5 ml 0.5% bupivacaine plus epinephrine 1:200,000 (which contains 12.5 mg bupivacaine and 12.5 µg epinephrine) was used; and in group B, 10 ml 0.125% bupivacaine plus epinephrine 1:800,000

was used (prepared by diluting 2.5 ml 0.5% bupivacaine plus epinephrine 1:200,000 with 7.5 ml sterile physiologic saline solution).

Dural puncture was performed using a 22-gauge needle at the L3-L4 interspace in the left lateral decubitus position with the operating table in the horizontal plane. After injection of local anesthetic over 30-45 seconds, the patients were turned supine and placed in the lithotomy position. Arterial blood pressure and heart rate were recorded automatically (Dinamap) before and during the first 20 minutes of the spinal anesthesia at 1-minute intervals. Hypotension was considered to be present when systolic blood pressure decreased by more than 30% from control or when it was lower than 90 mm Hg. The level of anesthesia was determined by pinprick at 2, 5, 10, 15, and 20 minutes, and the motor blockade was also evaluated at the same time intervals, using a 0-3 scale (0 = no motor blockade; 1 = hip flexion with extended leg blocked; 2 = knee flexion blocked; 3 = complete motor blockade). Postoperatively the degree of motor blockade was evaluated every 15 minutes to determine time to complete recovery of motor activity.

All results are expressed as mean \pm SEM. The two groups were compared statistically by analysis of variance for repeated measures; Students *t*-test for paired and nonpaired data was used subsequently. χ^2 analysis was used to compare the incidence of hypotension and incomplete anesthesia in both groups. A value of $P < 0.05$ was considered statistically significant.

Results

Age, height, and weight of patients were similar in both groups (Table 1). The extent of anesthesia was the same in both groups (Fig. 1). Onset of sensory block was rapid in both groups: within 2 minutes after the start of injection, a sensory level could be detected in all patients. Mean cephalad spread of

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Table 1. Bupivacaine Data and Patient Characteristics

Group	n	Bupivacaine			Epi (μ g)	Age (yr)	Height (cm)	Weight (kg)
		Conc. (%)	Vol (ml)	Dose (mg)				
A	25	0.5	2.5	12.5	12.5	70.5 \pm 1.6	173.0 \pm 1.3	76.5 \pm 2.5
B	25	0.125	10	12.5	12.5	67.5 \pm 2.6	173.3 \pm 1.5	71.9 \pm 1.9

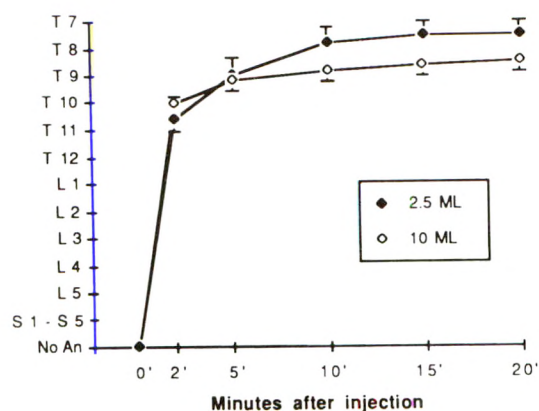
Mean \pm SEM.

Figure 1 Anesthetic level: extent of anesthesia after subarachnoid injection of 2.5 ml bupivacaine 0.5% plus epinephrine 1:200,000 (group A) or 10 ml bupivacaine 0.125% plus epinephrine 1:800,000 (group B). Each point represents mean \pm SEM.

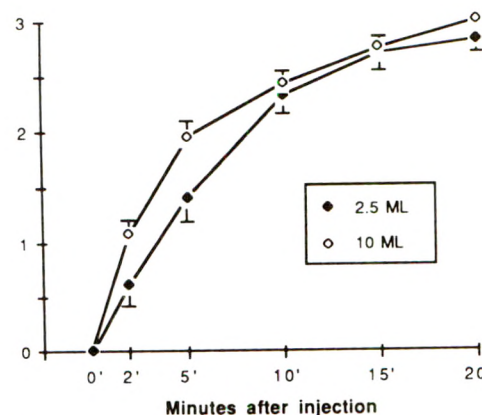


Figure 2 Motor blockade during spinal anesthesia produced by 2.5 ml bupivacaine 0.5% plus epinephrine 1:200,000 (group A) or 10 ml bupivacaine 0.125% plus epinephrine 1:800,000 (group B). Each point represents mean \pm SEM.

anesthesia after 20 minutes was similar in both groups ($T7.5 \pm 0.5$, range T1–T10 in group A, and $T8.6 \pm 0.4$, range T5–T11 in group B). Caudal spread always included the sacral segments. The highest cephalad spread observed was T1 in group A and T5 in group B.

In both groups, analgesia was adequate except in three patients (12%) in group A (2.5 ml); these patients required additional intravenous analgesics to permit surgery despite a sensory level that should have been adequate (T9, T9, and T10) and despite the absence of blind spots. The incidence of suboptimal anesthesia was not statistically different between the two groups. None of the other patients required sedatives or analgesics.

The degree of motor blockade was similar in both groups (Fig. 2). Motor blockade was complete in all patients within 20 minutes except for three patients in group A who had incomplete motor blockade of the lower extremities 20 minutes after subarachnoid injection of the local anesthetic. Duration of motor blockade was similar in both groups: 228 ± 8 minutes in group A and 237 ± 10 minutes in group B. The duration of sensory blockade always exceeded that of the motor blockade.

Heart rate and arterial blood pressure did not differ between the two groups (Figs. 3 and 4). A gradual

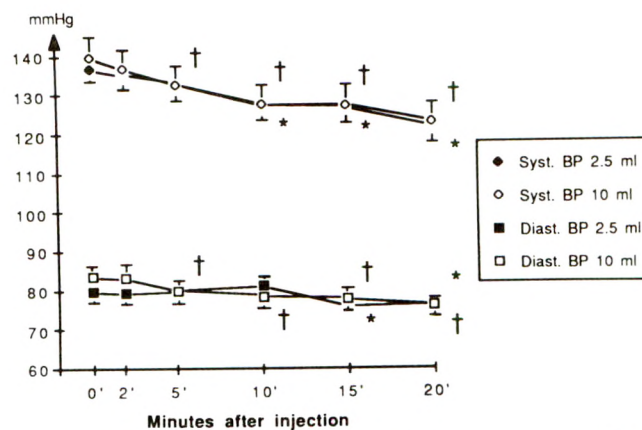


Figure 3 Systolic and diastolic blood pressures during spinal anesthesia produced by 2.5 ml bupivacaine 0.5% plus epinephrine 1:200,000 (group A) or 10 ml bupivacaine 0.125% plus epinephrine 1:800,000 (group B). Each point represents mean \pm SEM. * and $P < 0.05$ compared with baseline (0') in group A and group B, respectively.

decrease in arterial blood pressure was observed in both groups. Although mean levels of systolic blood pressure were similar in both groups, four patients in group A (16%) developed hypotension and were treated with administration of additional IV fluids, supplemented with ephedrine 10 mg IV if necessary. Only one patient in group B had hypotension. The incidence of hypotension in both groups was not

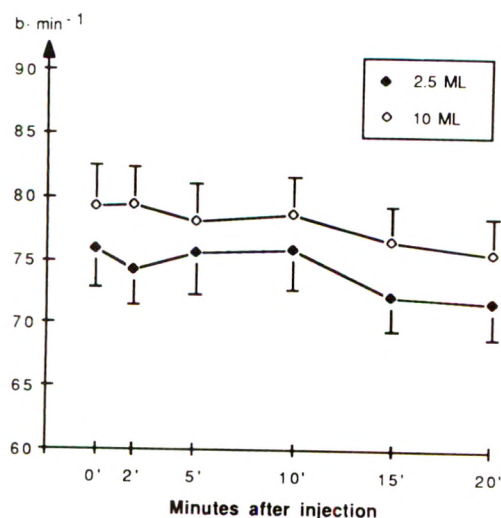


Figure 4 Heart rate during spinal anesthesia produced by 2.5 ml bupivacaine 0.5% plus epinephrine 1:200,000 (group A) or 10 ml bupivacaine 0.125% plus epinephrine 1:800,000 (group B). Each point represents mean \pm SEM.

different according to the χ^2 -test. No patient had bradycardia ($>20\%$ decrease in heart rate).

Discussion

The results of this investigation confirm that using different volumes or concentrations while maintaining a constant dose of bupivacaine during spinal anesthesia does not affect the extent of anesthesia; similar onset and extent of anesthesia and degree of motor blockade were found when using 12.5 mg bupivacaine with 12.5 μ g epinephrine dissolved in 2.5 or 10 ml of solution. The major difference when comparing this study with previous ones (1-7) is that we used widely different volumes (2.5 ml and 10 ml). We previously studied the effects of injecting 10 ml bupivacaine 0.125% plus epinephrine 1:800,000 in the subarachnoid space during the evaluation of this solution as a test dose for epidural anesthesia (8). In that study we found that it gave adequate anesthesia when injected intrathecally without significant side effects. Therefore we decided to study the effects of subarachnoid administration of this solution in greater detail.

The physical characteristics of spinal anesthetic solutions are major determinants of their spread in the cerebrospinal fluid (CSF). The most important characteristics are density, the amount of local anesthetic given (mg), the concentration of the anesthetic, and the volume of the anesthetic solution injected. A change in one of these four factors is always associated with a change in at least one of the other three

factors. Other determining factors are posture and site of injection (6). Specific gravity measured at 37°C is 1.0067 (± 0.0001) for bupivacaine 0.5% plus epinephrine 1:200,000, and 1.0061 (± 0.0001) for bupivacaine 0.125% plus epinephrine 1:800,000. Compared to the specific gravity of CSF at this temperature (1.0075-1.0063), the high-volume, low-concentration bupivacaine solution is slightly hypobaric in all patients, while the 0.5% bupivacaine solution is hypobaric in some, isobaric in others, and hyperbaric in still others.

In this study we did not observe either statistically or clinically significant differences between the two groups concerning onset of anesthesia, extent of anesthesia, or degree of motor blockade. Therefore, we can extend the conclusion of previous studies that volume or concentration of a local anesthetic does not affect the extent of anesthesia during spinal anesthesia; we showed that this conclusion is still valid when widely different volumes are used.

Although the extent of anesthesia was similar in both groups, we did observe that a more intense block was obtained using the larger volume, because in group A (2.5 ml) there were three patients with incomplete analgesia despite a satisfactory sensory level as determined by needle pinprick. The incidence of inadequate analgesia was not statistically different between the two groups. However, we have no satisfactory explanation for the inadequate analgesia in the presence of an anesthetic level that should have produced adequate anesthesia. It is possible that inadequate mixing of the local anesthetic with the CSF was present when the smaller volume was used. It has been stated previously (5,9) that low doses of 0.5% bupivacaine are associated with poorly predictable levels of anesthesia. Increasing the dose of bupivacaine increases the success rate (2) but also the extent of anesthesia (3), thereby increasing the incidence of hypotension (3). We can now suggest that using the same amount of bupivacaine in a larger volume (10 ml of 0.125%) could increase the success rate without creating a higher level of anesthesia and without increasing the risk of hypotension. It also improves predictability of the level of anesthesia, because extent of anesthesia had a slightly narrower range in the 10-ml group than in the 2.5-ml group. This may be due to specific gravity differences between the two solutions. Logan et al. (5) also found a narrower range when using a higher volume (4.0 ml vs 2.7 ml). McClure et al. (1), however, observed a less predictable blockade with an increased frequency of higher blockade and risk of hypotension when increasing the volume from 1 to 4 ml.

No differences in heart rate and systolic blood pressure were observed between the two groups, whereas absolute changes were small. This may be related to the position of the patients (lithotomy position) and thus an increased venous return, even without prior volume loading. It is also possible that sympathetic blockade during spinal anesthesia is less intense than previously thought (10). However, we did observe hypotension in four patients in group A and in only one patient in group B. These four patients in group A had a higher level of anesthesia (T4, T3, T1, T3) than the average patient in that group had, which may have caused more sympathetic fibers to be blocked.

We could not detect any neurologic complications after injecting volumes of anesthetic solutions into the subarachnoid space that were larger than anesthesiologists normally use. No patient complained of headache or had other signs or symptoms of increased intracranial pressure during or after intrathecal injection of the local anesthetic. This may be related to the low speed of injection.

It has been shown that adding epinephrine to the local anesthetic in spinal anesthesia prolongs the duration of sensory blockade and intensifies the blockade (11,12). However, in this study much smaller amounts of epinephrine (12.5 μ g) were used than in other studies (100–300 μ g), making it difficult to determine the role of epinephrine in this study.

In conclusion, the effects of volume and concentration of glucose-free bupivacaine in spinal anesthesia were investigated in 50 men undergoing transurethral surgery. Patients in group A ($n = 25$) received 2.5 ml 0.5% bupivacaine plus epinephrine 1:200,000, and patients in group B ($n = 25$) received 10 ml 0.125% bupivacaine plus epinephrine 1:800,000. It was found that during spinal anesthesia the volume or concentration of glucose-free bupivacaine, when a constant dose is maintained, does not affect the extent of anesthesia, degree of motor blockade, or hemodynamic changes, even when widely different

volumes are compared. However, a more predictable level of anesthesia was found when the 0.125% bupivacaine solution was used, maybe because this solution is hypobaric in all patients, in contrast to the 0.5% solution.

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Lateral Position and Epidural Anesthesia for Cesarean Section

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and Ghassem E. Larijani, PharmD

Key Words: ANESTHESIA—obstetric.
ANESTHETIC TECHNIQUES—epidural.

Because of the risks of aortocaval compression, term parturients should not lie supine. Consequently they are often kept in the lateral position or supine with left uterine displacement during induction of epidural anesthesia. After injection of small amounts (6–12 ml) of local anesthetic for analgesia during labor, spread of sensory blockade has been reported as greater on the dependent side (1,2), with the degree of analgesia on the nondependent side often being inadequate (2). In nonpregnant patients, blockade also develops more rapidly and to a greater extent on the dependent side after injection of larger volumes of local anesthetic (15–20 ml) (3–5). In this study we compared the onset and spread of epidural blockade on the dependent and nondependent sides in term parturients during induction of epidural anesthesia for cesarean section.

Methods

Thirty-five term parturients requesting epidural anesthesia for elective cesarean section participated in this protocol, which was approved by the institutional review board. We randomly assigned the women to lie on either their right (group R) or left (group L) side while we inserted a catheter into the epidural space via the L2–3 or L3–4 interspace. The women remained in the lateral position for 20 minutes during the induction of anesthesia and then assumed the supine position with left uterine displacement and were transferred to the operating table. Using 3% 2-chloroprocaine via the epidural catheter, we established epidural anesthesia in the following standardized manner: Initially we injected

3 ml and waited 3 minutes while observing for signs of intrathecal injection; we then injected 5 ml while inquiring about symptoms of intravenous injection. Subsequently we made three additional 5-ml injections at 60-second intervals, for a total dose of 23 ml. After 20 minutes, we gave additional drug if the spread of analgesia appeared slow. At 5-minute intervals beginning with the initial 3-ml injection, we determined the upper and lower extent of sensory analgesia on the right and left sides by measuring loss of sensation of sharpness in response to pinprick. Using Student's *t*-test for paired measures and Fisher's exact test, we examined our data for the presence of significant ($P < 0.05$) differences between the right and left lateral decubitus position as well as in the time of onset and the extent of blockade in dependent and nondependent spinal segments.

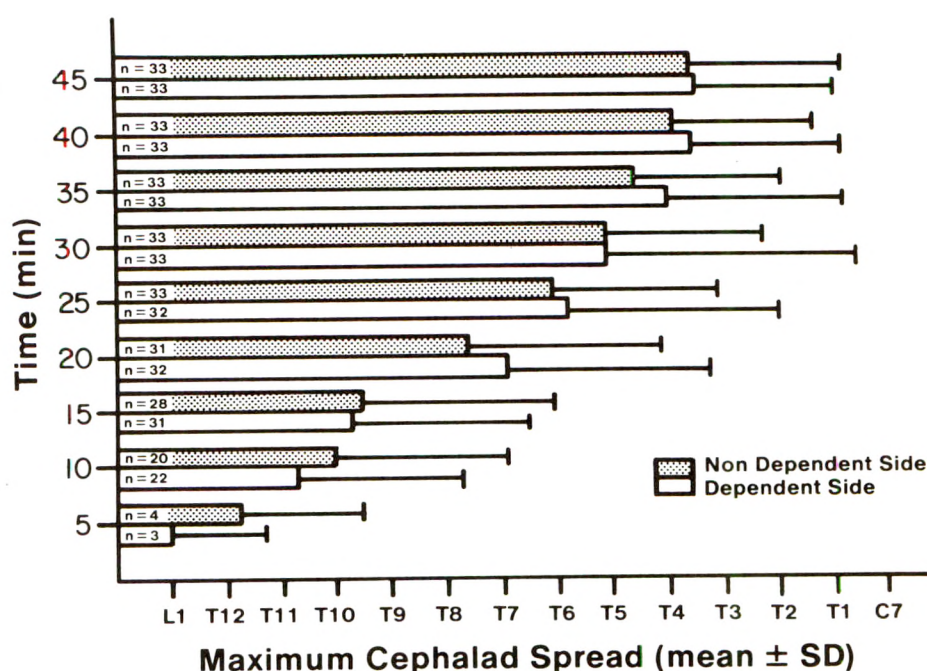
Results

Of the 35 patients participating in this study, 18 were in group L and 17 were in group R. Two of the patients in group R had unsatisfactory anesthesia (no sensory blockade in one patient and exclusively unilateral sensory blockade in another). We did not include the data from these patients in the study. Of the remaining patients, 12 in group L and 13 in group R required no additional analgesia before delivery, whereas the others received supplemental analgesia (N_2O and/or ketamine) before delivery. There were no statistically significant differences between groups R and L regarding time of onset or level of sensory blockade. Therefore, we combined both groups for further analysis of the influence of gravity on the onset and spread of analgesia. We could find no differences between the dependent and nondependent sides either in the cephalad spread of sensory blockade (Fig. 1) or in the total number of spinal segments blocked (Fig. 2) at any time. Sixteen of the 33 patients had equal cephalad spread of blockade, while nine patients had higher levels of sensory

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Figure 1 Maximum cephalad spread of epidural blockade measured at 5-minute intervals in 33 term parturients who remained in the lateral position for 20 minutes after epidural injection of 23 ml 3% chloroprocaine. Loss of sensitivity to pinprick was measured on the dependent and nondependent sides at 5-minute intervals for 45 minutes.



blockade on the dependent side and seven on the nondependent side.

Discussion

Several studies of nonpregnant patients have shown more rapid onset and greater spread of epidural blockade on the dependent side during induction of anesthesia in the lateral position (3-5). In the first study of this issue, Grundy et al. (3) injected 20 ml 0.75% bupivacaine at the L3-4 interspace. Their 12 patients remained in the left lateral decubitus position for 15 minutes after injection. Loss of sensation of pinprick sharpness (analgesia) occurred 1-4 minutes sooner at each segment on the dependent side. In addition, the level of sensory blockade was two segments more cephalad on the dependent side in 8 of the 12 patients. Subsequently, Apostolou et al. (4) confirmed these results in a study of 40 males who remained in the lateral position for 30-35 minutes after receiving epidural injections of 15 or 20 ml of 2% lidocaine with 1:200,000 epinephrine. Analgesia developed 1-2 minutes sooner on the dependent side than on the nondependent side and, as in the study by Grundy et al., the level of sensory blockade extended two segments more cephalad on the dependent side. More recently, Seow et al. (5) also found more rapid onset (1-3 minutes) and more cephalad spread of sensory blockade (0.3-1.1 segments) on the dependent side in 60 nonpregnant patients who remained in the lateral position only during injection

of epidural local anesthetic. Authors of these reports postulate that gravity encourages greater dependent spread of local anesthetic blockade when patients assume the lateral position during or after drug injection (3-5).

Studies of the effects of the lateral position on the spread of sensory blockade in pregnant patients have focused only on the spread of small volumes of local anesthetic used for pain relief during labor. Husemeyer and White (1) administered 10 ml 1.5% lidocaine epidurally in 34 term parturients who remained in the left lateral decubitus position for 10 minutes after injection. In these women the average number of spinal segments blocked was greater on the dependent side (12.1) than on the nondependent side (9.1) (1). Similarly, Rolbin et al. (2) found more dependent segments blocked (5.1 vs 3.4) in 15 laboring women who remained on their sides after injection of 6 ml 0.5% bupivacaine. Interestingly, in a further 50 women who remained on their sides after injection of 12 ml 0.25% bupivacaine, the spread of sensory blockade was more even (5.8 vs 5.0 segments blocked). However, despite the similar number of spinal segments blocked, these patients had better analgesia on the dependent side (2).

In our study, we found no differences in the time of onset or spread of sensory blockade between the dependent and nondependent sides after injection of 23 ml 3% 2-chloroprocaine. Indeed, while blockade was equal bilaterally in most patients, 7 of our 33 patients actually had more cephalad spread of sen-

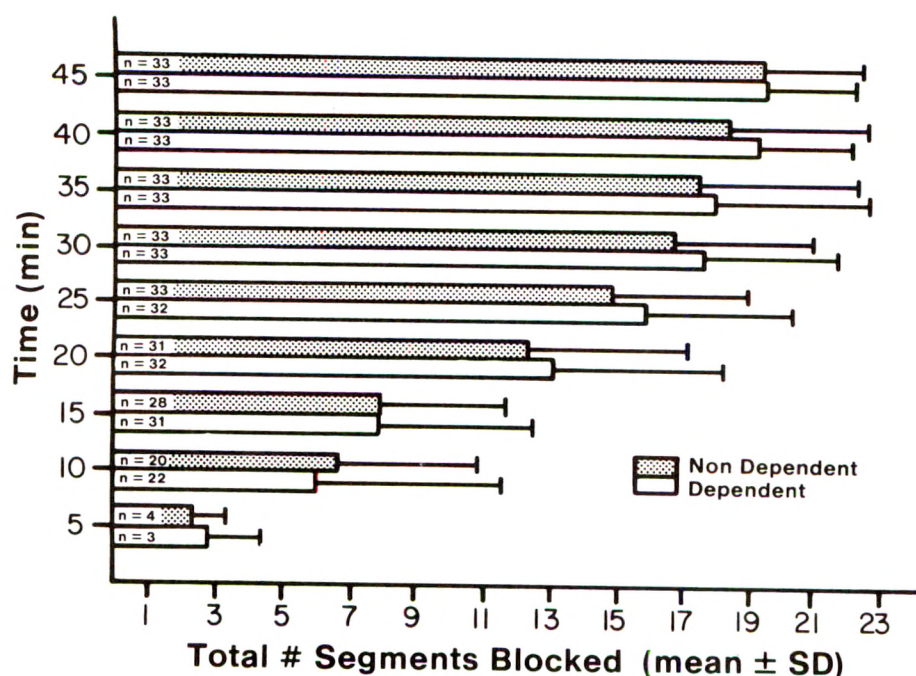


Figure 2 Total number of segments blocked after epidural injection of 23 ml of 3% 2-chloroprocaine in 33 parturients who remained in the lateral position for 20 minutes. Loss of sensitivity to pinprick was measured on the dependent and nondependent sides at 5-minute intervals for 45 minutes.

sory blockade on the nondependent side. These findings are in contrast to the findings discussed above for nonpregnant patients (3-5). Explanation for different findings in pregnant and nonpregnant patients may lie in the physiologic changes of pregnancy. The blood volume increases in pregnancy. In addition, the enlarging uterus obstructs blood flow through the inferior vena cava and shunts flow through the epidural veins (6). These two factors cause engorgement of epidural veins and may obstruct flow of local anesthetic in the epidural space. In the lateral position, both blood and CSF would pool slightly, possibly inhibiting access of injected local anesthetic to the nerve roots on the dependent side, counteracting the effects of gravity and encouraging a more even spread of blockade. This phenomenon may explain the varying results found after injection of small or large volumes of local anesthetics. Small volumes of solution (5-10 ml) seem to spread preferentially under the influence of gravity to the dependent side (1,2). However, as the volume injected increases (12 ml), the spread of sensory blockade becomes more even, but the intensity of block is still greater on the dependent side (2). As the volume injected increases still further (23 ml), the obstruction offered by the engorged epidural veins balances the effects of gravity, and the spread of sensory blockade is equal on both sides. Occasionally this venous engorgement may inhibit dependent spread to the point where higher cephalad spread of blockade develops on the nondependent side.

Alternatively, nerve fibers in pregnancy are more susceptible to local anesthetic blockade (7). This may render the nerves on the nondependent side susceptible to blockade despite exposure to smaller amounts of local anesthetic.

In summary, we found that gravity does not augment the spread of analgesia to pinprick in term parturients receiving epidural anesthesia for cesarean section. Therefore, ensuring adequate, bilateral blockade for cesarean section does not require postural manipulation.

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A Thin Fiberoptic Bronchoscope as an Aid to Occlusion of the Fistula in Infants with Tracheoesophageal Fistula

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Key Words: LUNG—tracheoesophageal fistula. ANESTHESIA, pediatric. EQUIPMENT—bronchoscope, fiberoptic.

The survival rate of otherwise healthy term neonates with esophageal atresia and distal tracheoesophageal fistula (EA/TEF) now approaches 100%, but morbidity and mortality remain high when there are associated major congenital anomalies, especially those related to the heart, or when pulmonary complications ensue (1). We (2) and others (3) have reported the use of a Fogarty balloon catheter for temporary occlusion of the fistula to allow recovery from respiratory insufficiency before any surgical correction of the EA/TEF is undertaken. We describe an illustrative case in which we found a new thin fiberoptic bronchoscope (diameter 2.0 mm) helpful in placing the Fogarty balloon catheter in the fistula via the stomach at the time of gastrostomy.

Methods

A fiberoptic bronchoscope with a diameter of 2.0 mm and a length of 60 mm (Microvasive, Inc., Milford, MA 01757, catalog no. 8320) is easily passed through an endotracheal tube with an inner diameter (ID) of 3 mm. It is possible to continue positive pressure ventilation at the same time, using a fiberoptic scope swivel adapter (Portex Inc., Wilmington, MA 01887, catalog no. 625207), which has a diaphragm through which the fiberoptic bronchoscope can be advanced down the endotracheal tube.

A standard 4F Fogarty balloon catheter has an external diameter (ED) of 0.95 mm, and the balloon, when fully inflated with 0.75 ml of air, has an ED of 5.0 mm. When the balloon is inflated in the distal

esophagus of a patient with EA/TEF it will effectively occlude the fistula, permitting positive pressure ventilation even in the patient with poor pulmonary compliance; it also prevents tracheobronchial aspiration from gastroesophageal reflux.

A full-term neonate with severe VATER association anomalies that included EA/TEF, anorectal agenesis, renal hypoplasia, multiple vertebral anomalies, atrial septal defect, and patent ductus arteriosus, was transferred to Duke University Medical Center at day 1 of life. In addition, she had severe congenital hydrocephalus. Her kidneys measured 1.3 cm and 1.7 cm in their longest dimension (normal: over 3 cm), and she did not produce urine during the first 24 hours of life. The patient had required endotracheal intubation and resuscitation in the delivery room and had been maintained on a low level of ventilatory support. Nevertheless, considerable gastric dilation by ventilating gases had occurred, threatening gastric rupture. Because the patient's ultimate survival was in doubt, repair of the EA/TEF was delayed, and gastrostomy to prevent gastric perforation was planned, along with colostomy at the same time. We elected to spare the infant immediate thoracotomy for repair of the EA/TEF until the prognosis for survival was more certain, especially in view of the apparent presence of renal dysfunction. We therefore used the method of Fogarty balloon occlusion of the TEF that we have previously described for use in those infants with severe respiratory dysfunction and EA/TEF (2,4).

The patient arrived in the operating room with a 3-mm ID endotracheal tube in situ. Anesthesia was induced and maintained with fentanyl. Pancuronium bromide provided neuromuscular blockade, and the lungs were ventilated with a mixture of oxygen and air. The inspired oxygen concentration was adjusted to maintain the Sao_2 in the region of 90%. The fiberoptic bronchoscope was passed down the endotracheal tube, and it was found that ventilation, as judged by breath sounds, vital signs, and Sao_2 , could be effectively maintained with the fiberoptic broncho-

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scope located within the lumen of the endotracheal tube.

The fistula was seen just to the left of the carina at the junction of the trachea and left main stem bronchus. The bronchoscope was passed into the fistula and advanced until, by transillumination in the epigastrium, it was seen to have entered the stomach. With the bronchoscope in place, an incision was made in the left upper quadrant of the abdomen. A purse string suture was placed in the gastric wall, a gastrostomy was performed, and the bronchoscope was advanced from the stomach into the incision on the abdominal wall. A 12F mushroomhead gastrostomy tube and 4F Fogarty balloon catheter were passed through a separate cutaneous stab wound incision. A silk ligature was tied to the bronchoscope and to the Fogarty balloon catheter, the bronchoscope then being retracted, pulling the Fogarty catheter into the esophagus and distal trachea. The silk ligature was left emerging through the diaphragm of the swivel adaptor until completion of the operation; the endotracheal tube was then removed and replaced alongside the ligature in the trachea. The Fogarty catheter was manipulated to place the balloon in the esophagus distal to the fistula site; proper positioning was assured by visualization through the bronchoscope.

The gastrostomy and colostomy were quickly completed. Following these procedures, formal bronchoscopy with the infant telescopic bronchoscope was performed to confirm proper positioning of the balloon, to assess the airway, and to assure the absence of additional fistulas. The balloon was inflated with a small amount of dilute contrast solution that allowed radiographic confirmation of the position of the balloon (Fig. 1).

Results

The balloon was inflated when required during the next several days, first to prevent reflux while in the Trendelenburg positioning during placement of a subclavian central venous catheter on the second day of life and, second, to assure effective ventilation during general anesthesia for placement of a ventriculoperitoneal shunt on the third day of life. After survival of the infant seemed likely, successful repair of the EA/TEF was accomplished on the ninth day of life, at which time the Fogarty catheter was removed. Despite limited renal function, the infant has done well and is now 6 months old.

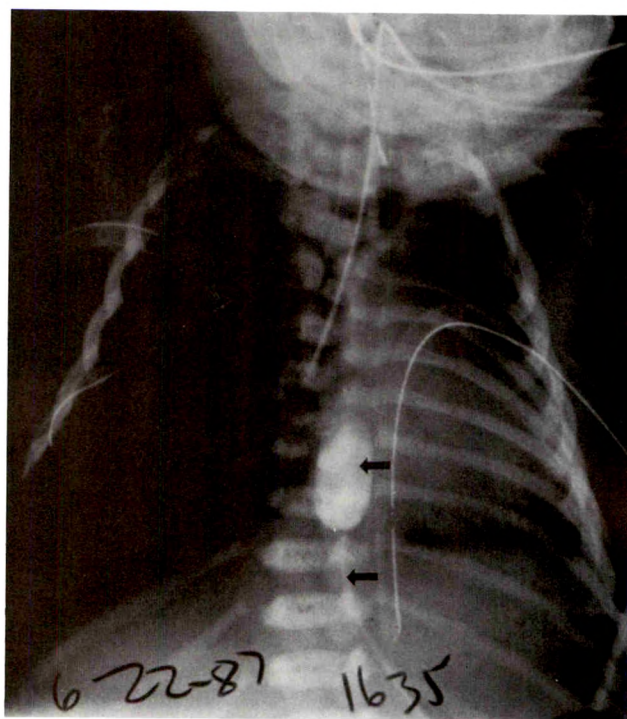


Figure 1. The inflated balloon of the Fogarty catheter (upper arrow) is in the distal esophagus with the shaft emerging caudad (lower arrow) via the gastrostomy.

Discussion

We avoid primary repair of EA/TEF in neonates who cannot maintain a Pao_2 of 60 mm Hg or better while breathing room air, having found this to be an important prognostic indicator (4). Neonates with EA/TEF and pulmonary problems such as pneumonia, meconium aspiration, or hyaline membrane disease may require ventilatory support for some time before they are suitable for surgery. Historically, these infants have done poorly when subjected to early thoracotomy and primary repair of the EA/TEF (5). When pulmonary compliance is poor, high inflation pressures may be required to achieve effective gas exchange; in such patients, the inflating gases may pass preferentially down the low-resistance pathway provided by the fistula into the stomach (6).

Karl (3) reported placement of a Fogarty catheter for occlusion of the distal esophagus through the gastrostomy, using cross-table lateral fluoroscopy in the operating room. Using this method of balloon placement, Berry (7) describes a case in which "the high pressures required for ventilation blew the Fogarty balloon down the esophagus into the stomach," necessitating an emergency thoracotomy to ligate the fistula. The proximal ligature we describe would in all probability have avoided this complication but, if not, it could have been used to reposition the balloon

under vision, thus avoiding the emergency procedure. We too have used this approach but have sometimes experienced difficulty in directing the Fogarty catheter into the gastroesophageal junction. The fiberoptic bronchoscope facilitates this and does not require fluoroscopic guidance.

We have previously reported the transtracheal approach to placement of a Fogarty balloon catheter (2,4). It requires a high degree of expertise on the part of the surgeon and the anesthesiologist, and necessitates interruption of ventilation for disconcerting periods of time. In addition, once the Fogarty catheter is in position, its shaft must share the cricoid ring (ID 4.7 mm in the average neonate) with the endotracheal tube. A 3-mm-ID endotracheal tube has an OD of 4.2 mm, and the shaft of a Fogarty balloon catheter has a diameter of 0.95 mm, thus raising the possibility of pressure necrosis at the cricoid level, though we have not had this occur in the ten patients in whom we have used this approach. Finally, the risk that the inflated balloon will be dislodged from the esophagus into the tracheal lumen is more likely when it enters the fistula from above; the catheter can be more securely tethered from below.

These problems have discouraged some and have led Templeton et al. (8) to conclude that the transtracheal approach may not be feasible in every case and to advocate early thoracotomy and ligation of the fistula in patients with progressive respiratory distress. We still consider the transtracheal approach the one of choice for those patients in whom compliance is so poor that effective ventilation is impossible and in whom oxygenation would be inadequate during the time required to perform a gastrostomy to position the Fogarty catheter from below. It can even be done in the intensive care unit if necessary, and the urgency of the situation would dictate our choice. We believe that the morbidity and mortality after thoracotomy and primary repair of the EA/TEF remains high in the infant with severe pulmonary dysfunction requiring high positive pressure support postoperatively, as has been shown repeatedly over many years (1,4,5).

We believe that the method described here is technically easier to perform and has several advantages over transtracheal placement. It is possible to define the lesion and to place the endotracheal tube optimally without rigid bronchoscopy; it is not necessary to interrupt ventilation at a critical time; the endotracheal tube does not have to share the cricoid

ring with the Fogarty catheter, but only with a fine ligature; and there is less likelihood of the balloon migrating cephalad into the tracheal lumen when the shaft is secured at the gastrostomy site. Moreover, if the balloon is displaced at any time, it can easily be rapidly repositioned by traction on the catheter from below or traction on the ligature from above, aided if necessary by fiberoptic visualization through the endotracheal tube. It is important, of course, to label the ligature and to make everyone caring for the patient aware of the mechanics of the balloon and of the hazards of it being malpositioned.

With the several methods now available for placing a Fogarty balloon catheter in the distal esophagus in patients with EA/TEF, we feel that urgent primary repair of compromised neonates is not indicated, that staged repair with several operations is not needed, and that one of these methods for balloon occlusion can be used in almost every instance. This will allow adequate evaluation of neonates with multiple congenital anomalies such as the one described here, and will permit recovery of adequate pulmonary function in those with respiratory insufficiency.

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Role of Lumbar Sympathectomy in the Pediatric Intensive Care Unit

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Key Words: ANESTHETIC TECHNIQUES, REGIONAL—sympathetic block, pediatric. ANESTHESIA—pediatric. SYMPATHETIC NERVOUS SYSTEM, BLOCKADE—pediatric.

Vascular access in the extremities of critically ill infants is a major problem that can lead to serious complications resulting from extravascular extravasation of potent vasoactive agents or arterial thrombosis and emboli caused by indwelling catheters. These complications respond poorly to conventional therapies, such as local heat, elevation of the extremity, and local application of vasodilators. In adults, vascular reconstructive bypass surgery may be undertaken, a therapeutic maneuver that may not be practical to the neonatal and infant populations.

Due to the limited success of present-day therapy in reversing severe ischemic complications in pediatric patients, the University of Miami Pain Service was consulted in the care of a number of critically ill infants with lower limb ischemia secondary to vascular cannulation. We present four patients with lower limb ischemia that were judged severe clinically. Only one of the four required more than a single-digit amputation after a series of percutaneous lumbar sympathetic blocks.

Methods

Percutaneous lumbar sympathectomies using 0.25% bupivacaine were all performed in the pediatric intensive care unit in the patients' bed after obtaining informed consent from the parents. Monitoring consisted of electrocardiogram, cuff blood pressure, and precordial stethoscope. Continuous intraarterial pressures was used for monitoring purposes when

present. The skin temperature was monitored in all toes as well as in the dorsum of the feet. An ultrasonic Doppler monitor was used to evaluate posterior tibial, dorsalis pedis, and femoral pulsations. All patients were adequately sedated.

Because the relation between the sympathetic nerve trunk and the spinal column remains constant throughout life, a well-described method for paravertebral sympathetic blocks in adults was adopted (1,2). The patients were placed in the lateral position. The spinous processes of L2, L3, and L4 were identified. As the last of the rami communicantes terminates at the L2 level, this vertebrae was chosen as the level of needle insertion.

A 22-gauge, 3.8-cm needle was inserted parallel to the spinous process, $1\frac{1}{2}$ to 2 cm lateral to the midline. The needle was directed at an angle of 30° to the midline and advanced until the vertebral body was contacted. The needle was then withdrawn to skin and the angle was progressively decreased until the needle grazed by the vertebral body anteriorly, at which point a distinct loss of tissue resistance could usually be felt. A dose of 3–5 ml of 0.25% bupivacaine was injected after careful aspiration. No evidence of complications, such as hypotension and drug toxicity, was noted during the procedures. In one patient (Case 1), an 18-gauge, 3.8-cm intravenous catheter was placed and secured for intermittent injections.

Report of Cases

Case 1

A 4-month-old female infant, who had survived a complicated neonatal course after delivery at 27 weeks gestation, had been doing well at home until she was brought to the emergency clinic at Jackson Memorial Hospital with a short history of lethargy and refusal to feed. She was severely ill on arrival and suffered a cardiopulmonary arrest from which she was successfully resuscitated. During resuscitation, a right saphenous vein cutdown was performed. The

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saphenous venous line subsequently infiltrated while calcium chloride was being infused resulting in an area of chemical cellulitis 3 cm in diameter on the medial aspect of her right calf. A provisional diagnosis of sepsis was made, and the patient was transferred to the pediatric intensive care unit (ICU).

A right-sided femoral cutdown was performed and both artery and vein were cannulated for monitoring and vascular access. In the next 24 hours, the right leg was found to be cool with decreased perfusion and sluggish capillary refill. Both cannulae were immediately removed. Weak femoral and popliteal pulses were present at that time. The dorsalis pedis pulse was absent. The tips of the toes were dark in color.

A right lumbar sympathetic block was performed. Thirty seconds after the block was completed, a dorsalis pedis pulsation was detected with the Doppler. A dramatic improvement in color and perfusion was seen. Skin temperature increased from a pre-block level of 31.8°C on the dorsum of the right foot to 33.5°C 5 minutes after the block. This favorable response was sustained for 4 hours. Eventually her femoral arterial pulses became intermittently detectable with gradual worsening of the perfusion and color in the limb. Although perfusion and color of the limb did not deteriorate to the level seen before the block, intermittent lumbar sympathetic blocks were performed using an 18-gauge catheter that was placed and secured. Injections of 2–3 ml of 0.25% bupivacaine through the catheter were performed three times during 24 hours with improvement being sustained over the subsequent 24 hours. At this point perfusion was well maintained without further blockade, and the catheter was removed. A 6-month follow-up revealed no apparent ill effects. The extremity was warm, well perfused, and fully functional.

Case 2

A 9-month-old baby girl with Down's syndrome was admitted to the pediatric intensive care unit after repair of an endocardial cushion defect. At the time of operation, left-sided femoral arterial and venous cannulas had been placed for monitoring purposes. On the second postoperative day, her left leg developed decreased arterial perfusion along with increased venous congestion. Both catheters were removed immediately, but there was no clinical improvement over the next 36 hours. At this time the foot was cold and blue with a weakly palpable femoral pulse. Popliteal, posterior tibial, or dorsalis pedis pulses

were neither palpable nor detectable with the Doppler probe.

A left-sided lumbar sympathetic block was performed resulting in immediate marked improvement in perfusion, color, and warmth in the lower leg and foot. Both femoral and popliteal Doppler pulses increased. Neither posterior tibial nor the dorsalis pedis pulses could be felt or detected by the Doppler probe. The effect lasted 3½ hours. The block was repeated on two subsequent occasions over the next 36 hours. After the last block, the dorsalis pedis pulse became palpable, and capillary refill was good. Ten days later, she was discharged with good perfusion and color in the limb despite foot pulses that were only barely palpable.

Case 3

A 2½-month-old girl with Down's syndrome entered the hospital with severe pulmonary edema requiring prolonged mechanical ventilation. Percutaneous arterial catheterization for blood gas monitoring became technically impossible and after cutdown procedures in both radial arteries, a second attempt at placement of a right femoral arterial line failed. Two days later, the entire right forefoot, particularly the right second toe, became puffy, cold, pale, and blue. She had evidence of two other small lesions consistent with emboli in the right forefoot. Echocardiography revealed no vegetations and, in the absence of embolic phenomena elsewhere in the body, the assumed site of origin of the emboli was thought to be the right femoral artery—presumably damaged during the failed attempt at cannulation.

A right lumbar sympathetic block was performed. An immediate result was improvement in the color and temperature at the foot. A 2.5°C temperature rise was noted within 2–5 minutes over four of the five toes. The right second toe remained unchanged. The patient had a prolonged ICU course but was eventually discharged home with a functional foot though the distal phalanx of the right second toe had to be amputated.

Case 4

A 2-year-old girl was admitted to the hospital with a short history of fever, lethargy, and vomiting. A diagnosis of H. influenza meningitis was made. On arrival, she was severely ill with low cardiac output state, high fever, and a fixed, dilated right pupil. A computerized scan revealed diffuse brain swelling.

On the second hospital day she developed a cold, blue left foot after an intravenous line that had infiltrated was removed. Doppler examination revealed absent dorsalis pedis and posterior tibial pulses. Initial treatment consisted of local nitroglycerine paste applied to the foot and O₂ therapy inside a hyperbaric chamber (2½ atm). Twenty-four hours later, the foot became darker in color. A left lumbar sympathetic block (without catheter placement) was performed before her next hyperbaric treatment. The foot became for the first time completely pink during hyperbaric O₂ therapy. Skin temperature increased from a preblock temperature of 26.1°C to 27.9°C. Sympathetic blocks and hyperbaric O₂ therapy were repeated on the following 2 days. On the third day, the cyanosis was no longer present, the pulses improved, and arterial perfusion was excellent. She was discharged after 10 days of therapy with an intact, fully functional foot.

Discussion

There is only a single previous case report of the use of sympathetic blockade to treat ischemic complications in pediatric patients (3). The present case studies represent the first reported use of percutaneous paravertebral lumbar sympathectomy to relieve severely compromised blood flow to the lower extremities in infants and small children.

It is known that lumbar sympathectomy produces vasomotor paralysis of the lower extremities which increases blood flow by decreasing peripheral vascular resistance. Sympathetic stimulation markedly reduces digital blood flow while sympathectomy increases it six to ten times (4). While it may be true that partial vasomotor tone returns after sympathectomy; nevertheless, total blood flow, as measured by Doppler methods, remains above the preblock level, except when reduced by occlusive processes such as atherosclerosis. This finding may explain the often poor results of lumbar sympathectomy in improving limb survival in adults, despite improvement in color and overall appearance of the limb, possibly because of shunting of blood through superficial venules (5).

Children, on the other hand, usually do not have intravascular disease. They may also have a more extensive collateral circulation than adults. However, the small vessels of children are particularly prone to thrombosis secondary to lowered cardiac output, polycythemia, and dehydration. Traumatic attempts at cannulation may result in a higher incidence of thrombosis than in the adults. Additionally, bypass surgery may be technically impossible.

The incidence of complications related to intravascular catheters in children is unknown. Clinical studies as well as autopsy reviews suggest that the incidence is higher than is generally believed (approximately 9%) (6,7). O'Neill et al. (7) reported on 16 children having severe ischemic complications associated with umbilical arterial catheters. Of these, ten required full-thickness skin grafts, two required split-thickness skin grafts, four developed gangrene that resulted in amputation, and one child died. Others have expressed concern that even though visible damage may not be evident, compromised blood flow to extremities in children may have long-term irreversible consequences in limb growth and development (9). Collateral flow may be responsible for limb survival, although there are no data on this.

The number of lumbar sympathectomy to improve collateral circulation in children has not been studied. The successful outcome in our four patients is encouraging. Lumbar sympathetic block may be useful in combination with hyperbaric O₂. This combination should complement each other because hyperbaric O₂ alone, while increasing the oxygen content of the blood, reduces systemic blood flow. The reduction in blood flow is due to a 20% increase in systemic vascular resistance (10).

Percutaneous paravertebral lumbar sympathetic blocks are associated with potential complications. These include puncture of major vessels or renal pelvis, subarachnoid injection, neuralgia, perforated intravertebral disc, and infection from the catheter technique (2). The possibility of toxicity of local anesthetic agents should not be ignored. It is imperative that an anesthesiologist should carry out the procedure.

In conclusion, a word of caution is needed. The indications for lumbar sympathectomy have not been studied in the pediatric population. Recognizing that this report relates to a small number of patients, it is, nevertheless, our belief that lumbar sympathectomy is effective in improving compromised blood flow of the lower limb and possibly in preventing tissue damage in pediatric patients with acute vascular occlusion.

We thank Dr. Emanuel M. Papper, Professor of the Department of Anesthesiology, University of Miami School of Medicine, along with Dr. N. W. Brian Craythorne, Professor and Chairman of the Department of Anesthesiology, University of Miami School of Medicine, for their expertise and guidance in the preparation of this manuscript. We also wish to thank Ms. Frances Solano for editorial and secretarial assistance.

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Letters to the Editor

Epidural Ketamine for Postoperative Analgesia

To the Editor:

We read with interest the report by Kawana et al. (1) of epidural ketamine for postoperative pain relief. We disagree with the authors' conclusion that epidural ketamine is not adequate for postoperative pain relief. We think that the authors should be more cautious and should state in their conclusion that they have used a lower dose range of ketamine epidurally (4 to 8 mg.). In our original work (2) we found that 10 mg ketamine in 10 ml of saline epidurally was ineffective in producing analgesia and all of the patients in that group required additional doses. The inadequacy of the small doses of ketamine epidurally has also been reported by Ravat et al. (3). Nevertheless we found that by increasing the dose of ketamine to 30 mg, 54% of the patients had adequate analgesia for 24 hours after a single epidural injection. Ravat et al. (3) also found in two pilot cases that 30 mg ketamine epidurally produced analgesia. The small number of patients (4) reported by Rubin et al. (4), in addition to the absence of the detailed description of methodology, make it difficult to draw any conclusion regarding the efficacy of the ketamine in their correspondence.

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Epidural Ketamine for Postoperative Pain Relief After Gynecologic Operations: A Double-Blind Study and Comparison with Epidural Morphine

In Response:

We appreciate Dr. Naguib's comments on our conclusions. We admit that our double-blind study with a control group receiving a placebo has demonstrated only that small doses (4 to 8 mg) of epidural ketamine were inadequate for postoperative pain relief after gynecologic operations (1). Because we did not use larger doses, we cannot comment on the effectiveness of a 30-mg dose of epidural ketamine.

When administering a drug epidurally, one might expect that a small dose would act directly and segmentally on the spinal cord, without systemic effects. Opiates are well-known examples of such drugs (2). However, Ravat et al. (3) reported in two pilot cases that 30 mg epidural ketamine had a sedative effect in addition to an analgesic action. In animal studies, the direct action of ketamine on the spinal cord is a matter of controversy (4-7). Mori et al. (7) refuted the direct action of ketamine on the spinal cord. Though there have been few pharmacokinetic studies of blood or CSF ketamine concentrations after epidural administration to date, it seems likely that large doses of ketamine, being absorbed systemically from the epidural space or moving cephalad in the CSF, act on the central nervous system rather than on the spinal analgesic system. The fact that intrathecal ketamine caused analgesia could be explained by its local anesthetic-like action (8).

We think that more pharmacokinetic studies in addition to animal studies are necessary to determine more fully the site of action and the effectiveness of epidural ketamine. We maintain that it is too early at this time to recommend the widespread use of epidural ketamine for postoperative pain relief.

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Data, Data Everywhere, and Not a Thought to Think

To the Editor:

In a recent article relating epidural morphine requirements to age during postoperative pain control, the authors offer evidence that generally agrees with most anesthesiologists' experience: There is an inverse relation between age and dose (1). However, I have some questions about treatment of the data. In Figure 1, the upper-left-most point is nearly 4 sds above the mean dose and more than 3 sds above the regression line. This outlier imparts considerable moment to the regression line and should be either explained or possibly discarded. Due to the large variation and possible contamination in these data, I suggest they may be better analyzed by the least median squares technique (2). There also appear to be outliers in Figure 2.

In Figures 2 and 3, the pain data seem to have been recorded only as whole numbers on a 0-10 scale and, as such, constitute ordinal measurements. These data cannot be properly analyzed using least mean squares regression, which requires an interval or ratio measurement scale.

In their discussion of data on pain during cough, the authors refer to a trend when the regression line slope was not statistically different from zero—not fair!

Finally, 66 patients were entered into the study. However, I cannot find 66 data points in any of the three figures. I doubt that these points are all obscured by the regression lines. If they are missing, we deserve an explanation. Note in particular the points around age 22. In Figure 1, there is one point. In Figure 2, there are two. In Figure 3, there are three. What is going on?

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In Response:

We thank Dr. Bourke for responding to our recently published article (1). However, the concerns raised about our statistical treatment of data are unfounded.

High variability in clinically obtained data is commonly encountered. This was discussed in the article at length. The data are easily obtained and we are confident of their accuracy. The patient in the upper left-hand corner of Figure 1 is plotted accurately. The data are not "contaminated," just variable. An important assumption in least mean square regression (LMS) is that variance of y is the same for any x . Heteroscedasticity is not obviously present in the scatter diagrams. We are less sanguine about discarding accurate data than is Dr. Bourke. A more valid concern would be the effect of the patients experiencing no pain on the regression lines. They tend to "dampen" any significant associations, so that our presented results may be viewed as conservative.

Dr. Bourke is mistakenly assuming that the scale of measurement determines the sampling distribution. One of the statistical assumptions implicit to LMS is that for any fixed value of x , y has a normal distribution. While continuous data are traditionally used for the dependent variable in LMS, ordinal data are not precluded. Dr. Bourke should recall that for suitably large sample sizes, the sampling distributions of binomial, exponential, and even rectangular distributions are approximately normal. Authoritative general statistical texts state that LMS is particularly robust to departures from the assumption of normality (2).

There are several reasons for not employing nonparametric analysis. Aside from the loss of information involved in ranking the data, nonparametric methods remain largely unfamiliar to medical journal readers. The techniques for distribution-free regression are graphical and not available on commercially available statistical software packages.

A trend such as that shown in Figure 3 can exist apart from statistical analysis. Statistics play but a supporting role. If the sample size had been doubled, the trend would have reached statistical significance. The trend shown in Figure 3 is slight, however. The only reason that $P = 0.05$ is used as a convention is that Sir R. A. Fisher, the greatest statistician, arbitrarily chose 5% as his critical level of significance.

We agree with Dr. Bourke that a number of data points are not identifiable on our figures. However, each of the Figures does contain 66 data points. Those which cannot be counted are either obscured by the regression lines or tightly grouped along the x -axes.

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Succinylcholine in Children

To the Editor:

Delphin et al. (1) report of an instance where the intravenous administration of succinylcholine to an infant was followed by cardiac arrest. The authors conclude that the use of succinylcholine adds a small risk to the patient and recommend that its use should be reevaluated. However, careful scrutiny of the report reveals that it is possible to draw conclusions that are at variance with those espoused by the authors.

The patient was 3 months old but the conceptual age was 43 weeks. Because average gestation is 40 weeks, it follows that the patient was born prematurely and, at that stage of development, was at increased risk of apnea during and after anesthesia. Current wisdom dictates that no anesthesia be administered to this patient for at least 6 months from birth, except for life-threatening emergencies. Thus, the first lesson is that, in view of the patient's prematurity, he should not have been placed at risk for a strictly elective procedure.

Nitrous oxide was administered to the patient. It is not clear why this was done, particularly in view of the fact that infants, especially premature infants, do better when managed with a mixture of N₂ and O₂ as the carrier gas for the volatile anesthetic.

A femoral venous catheter was inserted. It is easy to suggest that this was necessary in this patient because no other peripheral veins were available. But the point is that in an infant the repair of an uncomplicated inguinal hernia should require only 25-55 minutes of anesthesia. In light of this, what were then the reasons for subjecting the patient to the increased risks associated with femoral vein cannulation?

The patient was anesthetized, well oxygenated and easy to ventilate; why then the administration of succinylcholine? In a small, well anesthetized child, for an elective procedure there is no need to induce muscular paralysis (total to the point of apnea) for the sole purpose of intubation. Also, why such a large dose? The patient was given 2.1 mg/kg succinylcholine. Given the muscle mass/body weight ratio of an infant, where a larger fraction of the body weight is water, one could say that this dose is equivalent to 3.0 mg/kg or possibly 4.0 mg/kg in an adult. Very few would administer such large doses of succinylcholine to a healthy adult. What was the justification for injecting an equivalent dose in an immature infant?

I suggest that this article demonstrates that blind implementation of routines, as well as failure to appreciate the consequences of administering any drug or any patient, are sure prescriptions for anesthetic disasters.

Although I believe that succinylcholine need not have

been used in this infant, I hasten to add that I would be equally opposed to the use of any other paralyzing agent for the sole purpose of tracheal intubation (2). Also, in those cases where there should exist clear and preponderant indications for total muscular paralysis as the best and/or only means for accomplishing intubation, then the dose to be administered should be carefully calculated whether one uses depolarizing or nondepolarizing drugs.

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In Response

The recent report of a cardiac arrest in a pediatric patient with unrecognized Duchenne's muscular dystrophy prompted Delphin et al. (1) to recommend that elective use of succinylcholine (SCH) in pediatric patients be reevaluated, and they are not alone (2). I, too, would welcome this reevaluation, should it take the form of a large clinical prospective trial, particularly aimed at procedures lasting 15 minutes and requiring tracheal intubation. Delphin et al. recommend the use of succinylcholine only in rapid sequence inductions and in management of laryngospasm. Clearly, most patients at risk for hyperkalemia and other adverse side effects due to SCH can be identified preoperatively. Withholding SCH from a large group of patients to avoid extremely rare serious complications (i.e., hyperkalemic arrest) is acceptable only if the utilization of currently available nondepolarizing neuromuscular relaxants does not involve even minor additional risks. The recommendation that atracurium be used instead entails a slower onset and longer duration, the danger of unwanted early respiratory arrest should priming be attempted, histamine release with large bolus injections, and the dangers of failure to intubate and inadequate reversal, compounded by increased difficulty in assessment of reversal in the youngest patients. Reversal agents are also not without side effects, profuse salivation being quite common and contributing to laryngospasm after extubation.

Particularly, it is often difficult to assure that outpatient pediatric patients have indeed restricted oral intake and have an empty stomach. Until a nondepolarizing relaxant is available that has onset and duration characteristics comparable to SCH, or a large study has proven that a particular nondepolarizer has a greater risk/benefit ratio than SCH, particularly during short procedures, the "safest" relaxant remains to be defined and perhaps SCH should not be condemned prematurely. John Norman's 1982 editorial is still pertinent today: "Finally we still need a replacement for suxamethonium. Durant and Katz almost imply they are writing its obituary. Yet despite its many limitations and contraindications, few of us at the moment could manage without it. Is the pursuit of its replacement

like the search for the Holy Grail?" (3). The choice of intubation technique in elective pediatric patients is not always clear-cut, and individualization in each case remains paramount to safe anesthesia. One must be aware of all potential complications of each drug and be prepared to treat them. Unfounded avoidance of SCH in elective situations can amount to passing the buck from an elective setting into a critical one, where *restituto ad integrum* does not occur!

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To the Editor:

We read with interest the paper by Delphin et al. (1) concerning an abnormal reaction to succinylcholine (Sch) of a child suffering from Duchenne's muscular dystrophy. The authors mention myoglobin release after Sch and cite a 1971 observation of myoglobinemia association with Sch (2). In the course of the last few years, more light has been shed on the incidence of this phenomenon in healthy children by use of more sensitive methods for detection of the muscle pigment. This has led to the conclusion that the reaction appears to be of greater magnitude and incidence than previously recognized.

"Anesthesia-induced myoglobinuria" (AIM), visible and proven by laboratory analysis, was, in a systematic search, found to occur in 1 in 250 children (4 to 16 years of age) after the injection of Sch 1 mg/kg (3). Myoglobinuria, defined as a concentration > 300 ng/ml urine, was observed when the serum level was 3000 ng/ml and above (4). Hypermyoglobinemia can be detected in nearly 100% of patients given Sch 1 mg/kg (4,5). The maximal increase averaged 20 times pre-Sch baseline concentrations (5) and up to 100 times above baseline levels when two single doses of 1 mg/kg each were given 8 minutes apart (6). There was a significant correlation between the maximum serum alterations and CPK activity (5).

Myoglobin is not a neutral substance in regard to kidney function. Indeed, myoglobinuria and acute renal failure have been ascribed to use of Sch (7). Extensive release of myoglobin can be assumed in the case described by Delphin et al. in view of the increased CPK values in the perioperative period. Even without Sch or other drugs, the serum concentration of the pigment in myopathic disorders including Duchenne's muscular dystrophy is above levels seen in healthy control groups (8); in patients with Duchenne's muscular dystrophy there is, moreover, a significant correlation between CPK activity and myoglobin concentration (9).

Delphin et al. (1) propose reevaluation of the elective use of Sch in pediatric patients. We believe that the contraindications to Sch should be extended to cover cases in which a massive release of myoglobin after Sch is to be expected, such as previous AIM and probably myopathic disorders (6). This emphasizes the importance of the medical history and the preanesthetic physical examination. In cases of doubt, repetitive injections of Sch should be avoided due to their potentiation of the increase in serum levels of myoglobin (6).

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In Response:

In response to the letter of Dr. Boba we would like to clarify several of the issues addressed. Dr. Boba suggests that this infant, in view of his prematurity, was placed at risk for apnea during and after anesthesia for an elective procedure. We are aware of the current literature on this subject and the practice in our institution is to avoid elective surgery for 6 months from birth. This child's hernia had incarcerated multiple times prior to the scheduled procedure and, although scheduled electively, the procedure was believed to be urgent by his surgeon. Appropriate postoperative apnea monitoring was planned.

The administration of nitrous oxide during a halothane inhalation induction in an infant who is 3 months old and 43 weeks postconception has never been questioned in the existing literature. N₂O is useful as a carrier gas because it speeds induction.

As stated in our report, the saphenous vein catheter was placed during induction of anesthesia. The femoral intravenous catheter was placed during resuscitation.

The facilitation of endotracheal intubation is an indication for the use of a muscle relaxant. The dose of succinylcholine 2.1 mg/kg IV is not exceedingly large. It is established that infants appear to be relatively resistant to the

drug when the dose is determined on a mg/kg basis (1). This resistance is thought to be caused by the large volume of distribution in the infant due to a large extracellular fluid volume.

We certainly agree with Dr. Kempen that the use of succinylcholine cannot be entirely eliminated in spite of its risks as no replacement has been found in specific clinical situations. We look forward to a reevaluation in the form of a large prospective clinical study that can compare succinylcholine with its risks and benefits to those of short-acting nondepolarizing relaxants.

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Reference

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Pharmacokinetic Analysis of Succinylcholine-Cimetidine Interaction

To the Editor:

The recent communication by Ramzan (1) regarding pharmacokinetic analysis of succinylcholine-cimetidine interaction from the original data by Kambam et al. (2) contains one major flaw and two minor errors that render the conclusion pointless.

The flaw occurred when wrong reference points were used for the calculation of rate of recovery. After the administration of succinylcholine, the clinical response can be divided into three phases: 1) the phase of onset of action, i.e., the time between injection and complete twitch depression; 2) the phase of complete neuromuscular blockade, which starts at the end of phase one and ends when twitch starts to return; and 3) the recovery phase, i.e., the time between reappearance of twitch and full recovery. The rate of recovery (R) is a phenomenon of the recovery phase (3,4). Calculation of R requires at least two data points in the recovery phase in the integrated electromyographic response curve which, unfortunately, were not available. The data points chosen by Ramzan came from different phases, one in the phase of onset of action with 95% twitch depression, and another during phase of recovery with twitch height at 50%. The difference in the twitch height $95\% - 50\% = 45\%$ was divided by the duration of action (t) to generate the rate of recovery $R = 45\%/t$. Not surprisingly, then, the final calculation of txR lead to 0.45 in every case (except an error, see later). This is simple arithmetic. The use of statistics for numbers regenerated in such a manner is hardly necessary.

An arithmetic error was committed in Ramzan's analysis of Kambam's data (on the third patient in the cimetidine

group) such that txR or tx45%/t yields 0.36. This erroneous result was further used to support some elaborate discussion. Even if we disregard the flaw in the pharmacokinetic analysis (as described in second paragraph), this error would have invalidated part of his discussion. Also, the second reference in Ramzan's letter should read volume 32, not 33, of *Anesthesiology*.

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In Response:

In my analysis (1) of the data of Kambam et al. (2) it was assumed that incomplete (95%) paralysis was produced (no other data on degree of maximum paralysis was reported by these authors). If this value of 95% is incorrect then the duration (t) and rate of recovery (R) and the corresponding tR values will be different to that calculated by me.

Dr. Kao and colleagues (3) claim that the clinical response to succinylcholine can be divided into three phases. This will only be true if a supramaximal dose is given such that complete (100%) paralysis is produced and is maintained for some time. If a submaximal dose is given, then incomplete (for example, 95%) paralysis is obtained, from which spontaneous recovery at a constant rate occurs. This was assumed to be the case with the data reported by Kambam et al. (2).

The tR value for Patient 3 in the cimetidine group should read 45.04; thus, my discussion about the anomalous tR value for this patient is irrelevant. In addition, Reference 3 in my letter should read volume 32 of *Anesthesiology* as pointed out by Dr. Kao et al. (3).

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Book Reviews

Pediatric Cardiac Anesthesia

Carol L. Lake, MD, ed. Appleton & Lange, Norwalk, CT, 1987, 452 pp, \$69.00.

Anesthesia for repair and palliation of congenital heart disease has been an orphan field for many years. Despite the fact that the many different congenital heart disease lesions and their surgical treatment make up an innately more complex field than does the surgical treatment of acquired heart disease in adults, coverage of anesthetic management for treatment of congenital heart disease has been restricted to single chapters in cardiac or pediatric anesthesia texts. For the first time, the diverse, multidisciplinary information needed for optimal anesthetic management of these patients has been assembled into one textbook. Although this in itself would make the book a valuable contribution, the book is very well done overall and worth its price.

The book is multiauthored, drawing on anesthesiologists, cardiologists, and intensivists from a number of major pediatric cardiac centers in the United States and Canada. This format provides a good spectrum of approaches to anesthetic care and avoids the parochial approach of a single center or author. Dr. Lake has written four chapters by herself and each is extremely well researched and documented, with extensive references. The other chapters vary considerably in style, content, and erudition, but all do at least a creditable job and some of the chapters are outstanding.

Included are chapters on development of the heart, preoperative evaluation, cardiac catheterization, monitoring, and extracorporeal circulation. Separate chapters cover postoperative cardiac care, respiratory care, and general pediatric intensive care. Of the general chapters, those on pathophysiology of congenital heart disease, pharmacology of pediatric anesthesia, and myocardial preservation are outstanding. Lesions and their anesthetic management in each pathophysiologic category are covered in separate chapters. Each of these chapters is quite complete and well done. The chapter on anomalies of the pulmonary valve and pulmonary circulation is outstanding.

The field of congenital heart disease is so complex and developing so quickly that it is not surprising that some areas are not covered and, in other areas, coverage could be improved. Future editions (it is hoped there will be another edition of this valuable book in a few years) will need to be

larger to provide for this additional material. Coverage of the functional capacities of the immature heart in terms of biochemistry, electrophysiology, and ultrastructure is missing, especially as these relate to effects of preload, afterload, and rate on the performance of the immature heart. Intraoperative echo monitoring to assess adequacy of complex repairs and presence of residual defects is not mentioned, nor is the use of color Doppler with the 2-D echo to assess location, direction, and magnitude of intracardiac shunts. More coverage of the problems associated with anesthesia in the cardiac catheterization laboratory, especially problems associated with interventional cardiac catheterizations in congenital heart disease, would be useful. At present the book contains only a brief paragraph on sedation and anesthesia in the pediatric cardiac catheterization laboratory in the catheterization chapter that was written by two cardiologists!

Several chapters, including those on monitoring and extracorporeal circulation, do not adequately focus on specific pediatric issues and do not include a few studies from the literature that specifically address pediatric problems. Less general material that is available elsewhere and more coverage of specific problems in pediatric extracorporeal circulation and pediatric monitoring would be helpful. Additionally, in some of the chapters written by anesthesiologists, important and relevant material from the cardiology and cardiac surgery literature was not cited, leading to occasional misleading statements. The chapters on specific defects tend to rely too heavily on readily available anatomic surgical illustrations of defects. For anesthesiologists, pathophysiologic diagrams such as those used in the chapter on transposition of the great vessels give a better understanding of the whole circulation and the hemodynamic consequences of specific anesthetic and surgical interventions and manipulations. All these problems are minor, however, and detract little from the chapters cited.

The physical layout of the book is attractive and it is well bound although the print is rather small. Tables, diagrams, and illustrations are quite abundant and useful, with the exception noted earlier. Typos are few overall, except that one paragraph ended up in the middle of another.

There is a wealth of material presented in this book, sufficient so that beginning residents can readily profit from it. At the same time, even those who have much experience in pediatric cardiac anesthesia will find new and valuable information here.

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The Anesthesia Machine

Clayton Petty, New York: Churchill Livingstone, 1986,
234 pp, \$29.50.

This is a thoroughly referenced work which, as stated in the preface, is aimed at "anesthesiologists in private practice, medical students, nurse anesthetists, and residents." It presents a compendium of the manufacture, function, and hazards of the various parts which when combined form a modern anesthesia machine. An overview of the history of the development of the anesthesia machine and aspects of risk management and quality assurance related to the machine form a secondary focus. Much of the material about design and function is similar to that in a now out of print book (1), but the material has been considerably updated. This book's strengths lie in the detailed description of most of the internal parts of recent Drager and Ohmeda equipment, complete lists of tests required during manufacture, and complete references for those who would like to delve further. Weaknesses include poor quality of half-tone illustrations (photographs) and a dry descriptive writing style with infrequent references to current clinical practices. The emphasis on only two machines, one from each of two manufacturers, is evident throughout the text and may date the material quickly. Indeed, each of the two manufacturers already has a newer model available.

The book starts by tracing the development of the principal features of modern machines. However, in doing so it fails to give a sense of the difficulties in using ancient equipment and the important changes in practice permitted by improvements. The following chapter describes the production of an Ohmeda Modulus II, placing great emphasis on the importance and cost of quality assurance procedures. Test parameters are carefully described but the nature of the problems the tests are aiming to avoid and the methodology are not. The chapter would have been better placed toward the end of the book, after the reader was informed about the design and function of machine parts. Individual chapters devoted to each of the major components of the anesthesia machine contain copious detail about the design and appearance of the various parts. I would have preferred stronger emphasis on their function and interaction with the anesthetist and patient. For example, discussion of the problems in obtaining accurate measurements of low gas flows from standard rotameters would have benefited from mention of the difficulty in interpreting the relations between fresh gas composition and inspired gas composition because of O₂ consumption and anesthetic uptake during low-flow anesthesia.

There are occasional minor factual or semantic errors in discussions of physics and operating principles. For instance, the method by which minimal O₂ flow is achieved is incorrectly attributed to a stop on the needle valve collar

rather than to the presence of a flow resistor in parallel with the valve. The chapter on CO₂ absorption methods and anesthesia circuits show a bias for Bain and other modified Mapleson D circuits vs circle systems because the former are valveless. This bias is not carried through to the discussion of scavenging systems where valveless construction is perhaps more important. The concluding chapter on risk management and quality assurance presents an appropriate common-sense approach to maintaining and documenting anesthesia machine performance.

In summary, *The Anesthesia Machine* offers, in a single volume, comprehensive descriptive information about many important facets of anesthesia machine design and manufacture. While its dry style, descriptive approach, and detailed lists of manufacturing and testing specifications may make it inappropriate for the neophyte anesthetist, the experienced anesthetist would be hard put to find a better source for important reference material about the manufacturing and testing of anesthesia machines and their components.

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Anesthesia for Cardiac Surgery and Allied Procedures

Gothard JWW and Branthwaite MA. Boston: Blackwell Scientific Publications, 1987, 285 pp, \$69.50.

With the plethora of books available on cardiac anesthesia, one might properly ask, "Do we need yet another book for cardiac anesthetists?" If the book in question is *Anesthesia for Cardiac Surgery and Allied Procedures*, I would answer yes, especially for cardiac anesthesia trainees. This book is one of the "originals" in cardiac anesthesia. The first edition was published in 1977 and became a standard reference work at least in England.

This is not a scholarly "definitive" textbook, nor a hefty "manual" written in outline form. Rather, this small, didactic textbook is meant to provide guidance for the "trainee . . . based on the application of physiological principles." The most appreciative readers will be those receiving a new or renewed exposure to the cardiac surgical operating suite and faced with the task of absorbing large amounts of information concerning hemodynamic monitoring, cardiovascular physiology, and complex surgical techniques. References are not noted in the text, but are listed by topic at the end of each chapter. These seem up to date and include papers from a wide variety of basic science and clinical journals.

The book is arranged in ten logically organized chapters. The first two cover applied circulatory physiology and pathophysiology of cardiac disease. A large amount of

information is presented in succinct and readable form. Excellent figures are reproduced from basic scientific journals and well-known physiology texts. Noteworthy in this section is the excellent discussion of interdependence of the right and left sides of the heart, using ventricular function curves for both normal and abnormal states.

"Cardiac Diagnostic Techniques" is a brief overview of both noninvasive and invasive methods with emphasis on cardiac catheterization and angiocardiology. Particularly lucid are discussions of intracardiac pressures, significance of oxygen saturations, and complications of catheterization and angiocardiology. "Preoperative Assessment and Preparation" is a short chapter that emphasizes clinical cardiopulmonary evaluation and principles of premedication for adult patients.

"Principles of Anesthesia for Open Heart Surgery" covers choice of anesthetic technique and monitoring for adult patients. General principles of induction, muscle relaxation, intubation, maintenance of anesthesia, and ventilation are presented not in a rigid "how-we-do-it" style but with the idea that "anesthetic agents with very different properties can be used safely, provided their cardiovascular effects are understood." Overall, there were very few typographical errors in this book but they did seem to be clustered in the references to this chapter.

The material covering management of cardiopulmonary bypass, which includes parts of chapter five, all of chapter six, "Cardiopulmonary Bypass Techniques, Apparatus and Management," and parts of chapter seven, "Management After Cardiopulmonary Bypass," are good introductions for the novice. Several areas of controversy, most notably cerebral protection, are mentioned but not discussed in depth. The purpose of this section, which is to present the nuts and bolts of cardiopulmonary bypass, is achieved. Included are discussions of venous drainage, intracardiac suction, the ventricular vent, arterial cannulation, oxygenators, circuit priming, and temperature correction for arterial blood gas analysis.

I do have several minor criticisms of this section. First, in a discussion of the principles of the combined use of inotropic and vasodilator drugs (e.g., epinephrine and nitroglycerin), the author states that "a common principle is to aim by pharmacological means to simulate aortic counterpulsation. . . ." It is impossible to "simulate" pharmacologically the aortic balloon pump when giving a drug that increases myocardial oxygen demand. Only the mechanical support provided by the intraaortic balloon is able to "separate" myocardial oxygen demand and decrease it while increasing myocardial blood supply. This brings me to my second criticism: namely, the fact that the discussion of intraaortic balloon pumping is inadequate. There are no examples of augmented arterial waveforms, and no discussion of the principles of balloon inflation-deflation timing.

"Implications of Some Specific Conditions" contains an excellent discussion of chronic mitral and aortic valve disease, as well as considerations for multiple valve replacement, reoperation for valve disease, and emergency open-heart surgery. The finale is a clear but lengthy discus-

sion of resuscitation and anesthetic management for pulmonary embolism. "Anesthesia for Closed Cardiac Procedures" discusses anesthesia for surgery on the thoracic aorta, but is especially useful for the section on the pathophysiology and management of acute cardiac tamponade and chronic constrictive pericarditis.

"Congenital Heart Disease and the Principles of Pediatric Cardiac Surgery," the longest chapter at 50 pages, is divided into two parts. Part I, "Diagnosis," includes a good overview of sedation and anesthesia for cardiac catheterization. This chapter's strengths are found in Part II, "General Principles of Anesthesia for Operative Procedures in Children," particularly the section on closed cardiac surgery in infants and neonates. The sections on pediatric open-heart surgery and implications of specific conditions are adequate for the trainee observing occasional cases, but senior trainees and fellows will need to consult more specialized texts.

This book has much to recommend it to the trainee getting his or her first exposure to cardiac anesthesia, and to the practitioner who must get reacquainted with this field. The book is compact, concise, useful, eminently readable and, best of all, can be read and even reread during an initial two- or three-week rotation through cardiac anesthesia. In combination with a well-chosen selection of primary literature sources this book can provide a solid foundation for the cardiac anesthesia trainee.

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The ECG in Anesthesia and Critical Care

Daniel M. Thys. New York: Churchill Livingstone, 1987, 267 pp, \$24.00.

The ECG is perhaps the most widely ordered test in the hospital setting. Having an understanding of the information the ECG provides is essential to the anesthesiologist. From preoperative rounds to acute changes postoperatively, anesthesiologists must be able to rapidly evaluate the ECG. Although numerous texts and chapters present volumes of information on the subject, this book, *The ECG in Anesthesia and Critical Care*, is one of very few to approach the subject primarily from the viewpoint of an anesthesiologist. Although it is a comprehensive text involving numerous authors, the material does not overwhelm the reader.

The text may be too involved for the medical student. However, for the resident or staff anesthesiologist, the text covers the subject very appropriately. The initial chapters spend enough time on the basics to provide a thorough review of important physiologic principles. The next few chapters concern themselves with perioperative occurrences (arrhythmias, ischemia, etc.) and their diagnoses. Most clinicians should find this material useful and applicable to their everyday practice. The strongest chapters of the text are the ones on intraoperative arrhythmias and

ischemia. Presented in almost an outline format, they are extremely well written and are recommended for all clinical anesthesiologists. Leaving no stone unturned, the final chapters cover a variety of subject areas endearing to the subspecialist. They approach the broad subject matter with brevity and clarity. The manuscript is well referenced, supplying ample resources for further study. Despite some chapters' multiauthored approach, the text flows well and is easily digested.

My primary criticism revolves around the apparent confusing order of the chapters (e.g., chapter 7, "Basic Cellular Electrophysiology of the Heart" might be more appropriate ahead of chapter 4, "Conduction Defects" rather than following chapter 6, "Preop Diagnosis of Myocardial Ischemia").

The book presents an anesthesiologist's approach to a common problem, and should be judged as such. Clinical anesthesiologists will find it appropriate and informative. Suggested audience: senior residents and staff physicians.

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ECG Stat: Hospital Electrocardiography in Urgent Situations

John J. Edmonds Jr. Philadelphia: Lea & Febiger, 1988, 189 pp.

This manuscript, created by the director of the Bowman Gray Medical Center Heart Station, Dr. John Edmonds, presents a thoughtful review in rhythm strip understanding and interpretation. His approach to ECG interpretation breaks down a complex subject into an easily understood algorithm. This makes ECG interpretation a logical sequence that may be employed equally well by the intern as well as the seasoned clinician. The text starts with easily understood diagrams concerning sources of dysrhythmias and proceeds to delineate supraventricular dysrhythmias from ventricular, narrow QRS complexes from wide, tachyarrhythmias from bradyarrhythmias, and so on. Every abnormality is accompanied by a concise explanation and a rhythm strip. Fortunately, the ECG strips are reproduced very well and are easily read. Explanations are included and specific defects are clearly identified.

Unfortunately, the discussion on pacemakers primarily directs itself at pacemaker malfunction, rather than indications for placement, and as such is not particularly well suited to the anesthesiology audience. The chapter on antiarrhythmic drugs classifies those drugs, but lacks appropriate details concerning treatment. Hence, this chapter fails to address an area of concern to anesthesiologists.

The introduction states that this text focuses primarily on interpreting ECG abnormalities, and as such it is an excellent text. It supplies a method of interpretation that any clinician will find useful, particularly those lacking in formal cardiology training. Suggested audience: junior residents and rotators.

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Neurologic and Neurosurgical Intensive Care, 2nd Edition

Ropper AH and Kennedy, SF. Rockville, MD: Aspen Publishers, 1988, 364 pp, 52.00.

The discipline of neurologic and neurosurgical intensive care has developed more slowly than respiratory or cardiovascular intensive care. For many acute neurologic illnesses, there is no consensus regarding appropriate management or monitoring. Because of the explosive growth in the basic scientific understanding of ischemic and traumatic injury, many potentially useful clinical strategies have yet to be tested. Presumably, many will ultimately be of little value, because of the limited tolerance of the central nervous system to extreme changes in blood flow and metabolism. This book competently reviews the broad range of potential topics and provides a concise, practical summary of important concepts. Although multiauthored, the text flows smoothly throughout almost all chapters and consistently emphasizes important information with useful, up-to-date reference articles.

The text is most appropriate for physicians with modest previous exposure to neurophysiologic and neuropathologic problems. Consequently, it is invaluable for the intensive care physician who primarily treats non-neurologic problems or the house officer in anesthesiology, surgery, or internal medicine who requires a manageably brief summary of current information regarding critical neurologic illness. The chapters entitled, "Physiology and Clinical Aspects of Raised Intracranial Pressure" and "Treatment of Intracranial Hypertension" provide excellent introductions to the clinical problems likely to be least well understood by those who have not previously cared for critically ill neurologic and neurosurgical patients. Similarly, Part II of the book, entitled "Management of Specific Problems in the Neurological-Neurosurgical Intensive Care Unit," will be a valuable reference text for physicians who work in surgical or medical ICUs that admit only a small number of neurologic patients.

Perhaps one of the greatest strengths of the book is its emphasis on the extensive experience of the faculty at the Massachusetts General Hospital. In a field with many unanswered questions regarding basic mechanisms of injury and the influence of monitoring and therapy on outcome, prudent suggestions based on the careful observations and clinical investigations of a distinguished multidisciplinary group are valuable. Supplemented as those opinions are by a pertinent review of current literature, the clinical insights are kept in careful perspective. In nearly every area in which there is controversy or inconclusive data, the authors clearly identify the limitations of available information.

The textbook does have some weaknesses, most occur-

ring as a result of dealing with a field that includes so many diverse disciplines. The coverage of common respiratory and cardiovascular problems is superficial. Although the extent of cardiopulmonary detail would be appropriate as an overview for neurologists or neurosurgeons with minimal experience with ventilatory management or cardiovascular manipulation, it is likely that such individuals would prefer more exhaustive neurologic material. There is also little information regarding the management of several common problems in the acutely neurologically impaired patient such as sepsis, and the evaluation of fever. One might also wish for a summary of important therapeutic conflicts, such as the frequent problem posed by the concurrent desire to restrict fluids and provide adequate tissue perfusion. Nevertheless, these are minor complaints about a book that, because of its brevity, could not possibly satisfy every need.

Perhaps the most valuable aspect of the book is Part II, in which a variety of common neurologic problems are discussed in a succinct, lucid fashion. Several of the chapters are models of clarity and will no doubt serve as suggested reading for many house officers working in intensive care units. The chapters on severe head injury, nontraumatic brain hemorrhage, subarachnoid hemorrhage, and coma after cardiac arrest are particularly useful for this purpose. In those chapters, the balance between concise didactic material and well-chosen bibliographic material is laudable and reflects scrupulous editorial supervision.

In summary, the second edition of *Neurologic and Neurosurgical Intensive Care* is an excellent introductory and review text. It should be welcome in the library of every critical care physician and should be required reading for house officers starting out in specialties that require a working knowledge of the management of patients with acute neurologic illness.

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Principles and Practice of Regional Anesthesia.

Wildsmith JAW and EN Armitage. New York: Churchill Livingstone, 1987, 200 pp, \$65.00.

This book is intended for a British audience and the written text provides a basis for the reintroduction of regional techniques into the practice of anesthetists. The drawings are excellent, adding dimension and a unique, elegant portrayal of regional anatomy to an often scant and stilted text.

Beginning with an historical overview, the book outlines reasons for the lack of acceptance and successful practice of regional anesthesia in Great Britain. The chapter on local anesthetic pharmacology provides a cohesive review, in stark contrast to the chapters on pain pathways and autonomic blocks, which do not convey an overall understanding of the subject matter.

The majority of the book deals with spinal, epidural, and caudal anesthesia despite various other chapter headings. The references cited for each chapter and their textual review provide a solid basis for comparison of regional and general anesthetic techniques with regard to quality of anesthesia, patient and surgeon acceptance, and the influence of anesthesia on postoperative morbidity and mortality. From that standpoint, the book is an excellent primer from which to begin to answer questions of choice regarding general vs regional techniques.

This orientation is also the major limiting factor in the overall usefulness of the book. Techniques for performance of major nerve blocks are presented for the right-handed operator only. The photographs reflect the technical bias of the editors rather than further illuminating the relation of surface anatomy to successful visualization and needle passage through tissue planes. Most of the peripheral nerve blocks are left undescribed, reportedly because of a high degree of difficulty associated with their performance. A rigorous description of peripheral nerve block techniques would add versatility and greater utility to the text and to the practice of regional anesthesia in Great Britain and abroad.

To conclude, this is a beautifully produced review of spinal, epidural and caudal anesthetic techniques which also includes some unique conceptualizations of regional anatomy in the form of drawings by Patrick Elliot. The book succeeds at discussing the pros and cons of regional anesthesia, but fails as a substitute for already existing American and Scandinavian primers on the actual performance of regional block techniques.

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Clinical Anesthesia Procedures of the Massachusetts General Hospital. Third Edition.

Leonard L. Firestone, Philip W. Lebowitz, and Charles E. Cook, eds. Boston: Little, Brown, 1988, 728 pages, \$18.50.

This is the third edition of this pocket manual of anesthesiology procedures of the Massachusetts General Hospital. The emphasis, as with the previous editions, remains "the practical 'fundamentals' involved in administering anesthesia." In accordance with the ever expanding realm of anesthesiology as a medical specialty, the book continues to grow. There are new chapters on the preanesthetic evaluation of pulmonary, endocrine, and infectious diseases, as well as safety in anesthesia, ambulatory procedures, trauma, recovery room care, and pain. The book has been reorganized into three sections covering preanesthetic evaluation, administration of anesthesia, and patient care in other settings. The presentation of information has accordingly improved and reads more easily. The third edition is more than 130 pages longer than its predecessor. Despite this, the physical size remains the same so that it will still fit in a pocket of the ubiquitous white coat. This expansion of

text was obviously accomplished by printing on thinner paper. This is something that can only be taken so far and is a serious consideration if the next edition expands as much as this one.

In addition to the new chapters mentioned earlier there has been a great deal of updating of material in most areas of the book. New medications, instrumentation, and procedures are included where indicated. A number of informative new tables and diagrams have been added. Unfortunately some of the more useful tables have been eliminated such as the "Neonatal Pharmacopoeia" from the chapter on newborn intensive care. The inside front cover now contains the MHAUS recommendations for the treatment of Malignant Hyperthermia and the MH Hotline phone number. This is an excellent addition and is in an appropriate place. Inside the back cover is a Siggaard-Andersen nomogram. Most of our residents have used this space in previous editions to make an index of pertinent tables found in the text, such as infusion rates for sympathomimetic and vasodilating drugs. An index of tables for quick reference would have been more beneficial.

The text is written as a guide for the inexperienced resident managing patients. Although the experienced clinician may choose a management plan different from that outlined in the book, it gives the resident unfamiliar with a particular procedure a good basis on which to make decisions. It also acts as an excellent springboard for case discussions. In addition, the basic outline could serve as a guide in preparing for the written boards in anesthesiology. It contains a wealth of information for the new practitioner in anesthesia at an appropriate price. It remains a reliable quick reference for the medical student, nurse, and resident learning anesthesia.

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A Tribute to Professor Sir Robert Macintosh for his 90th Birthday.

W. D. A. Smith and G. M. C. Paterson, eds. Wolfeboro, NH: Longwood, 1988, 44 pp.

This *vade mecum* consists of richly deserved kudos, offered by those who know him best, to Sir Robert Macintosh, Oxford's Nuffield Professor of Anaesthetics Emeritus and a hero of 20th Century anesthesia, on the occasion of his 90th birthday.

Brief, yes, but exquisitely written, the tributes constitute a unique history of anesthesia while providing touching insight into the accomplishments and personality of an astonishing individual. After a foreword by Professor Sir Gordon Robson, President of the Royal Society of Medicine (RSM), opening remarks by Dr. W. D. A. Smith, president of the Section of Anaesthetics of the RSM, and an introduction by Professor Keith Sykes of the Nuffield Department of Anaesthetics, Dr. James Parkhouse summarizes Sir Rob-

ert's contributions to academic anesthesia. Dr. Parkhouse was First Assistant in Dr. Macintosh's department in Oxford from 1958 to 1967, before becoming Professor of Anaesthetics at the University of Manitoba in Winnipeg. He subsequently returned to the U.K. as Professor of Anaesthetics in Manchester and then became Professor of Postgraduate Medical Education in Newcastle before assuming his present position as Director of the Medical Careers Research Group at the Churchill Hospital.

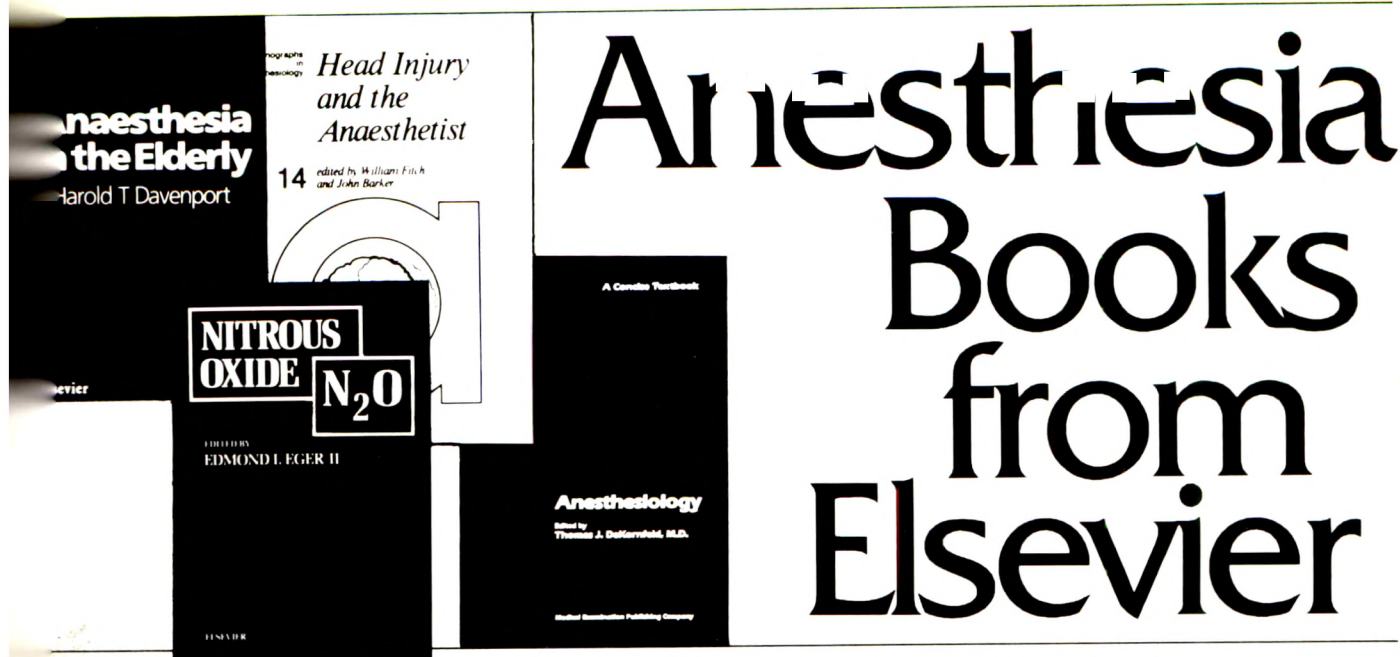
Dr. Parkhouse's contribute is followed by Dr. H. G. Epstein's. Dr. Epstein is the one who introduced physics to anesthesia, and vice versa. He did so not only through the classic *Physics for the Anaesthetist*, of which he and Drs. Mushin and Macintosh were coauthors, but also through his contributions to the scientific development of vaporizers that, still used, bear both his and Oxford's names. The next tribute comes from Dr. Thomas Boulton, consultant to the Nuffield Department. Dr. Boulton reviews one of Sir Robert's many major contributions in anesthesia, namely, draw-over anesthesia with ambient air. This may be a contribution barely known in North America, but it is a contribution widely known and appreciated throughout the rest of the world, and nowhere more so than in Third World countries.

Dr. Boulton's soliloquy is followed in turn by a resume of Sir Robert's contributions to regional anesthesia offered by Dr. Roger Bryce-Smith. Dr. Bryce-Smith was associated with the Nuffield Department at the time that Dr. Macintosh authored yet another classic, *Lumbar Puncture and Spinal Anaesthesia*. Oxford and, perhaps equally, the Royal Infirmary in Edinburgh, were almost the only places still using spinal and other forms of regional during the 1950-1975 Dark Ages of regional anesthesia in the U.K. when no regional anesthesia was being given throughout the rest of the country.

Next, Dr. John Lloyd, a consultant to the Nuffield Department, describes Sir Robert's role in the development, training, and acceptance of anesthetics nurses, an aspect of Sir Robert's career that will come as somewhat of a surprise to most anesthetists West of the 45th meridian. We then hear from Professor Alex Crampton Smith what it was like to be the successor to Sir Robert as the Nuffield Professor (1965-1980). Dr. J. Alfred Lee summarizes the role Sir Robert played in the Royal Society of Medicine and is followed by closing remarks and greetings offered by Professor Jan Lassner, President of the European Academy of Anaesthesiology, Dr. Aileen Adams, Dean of the Faculty of Anaesthetists of the Royal College of Surgeons of England, and Dr. Maurice Burrows, President-elect of the Association of Anaesthetists of Great Britain and Ireland.

A coruscating gem, this is a booklet that should be read by anesthetists of every age and level of training everywhere. It won't take long to read. It will never be forgotten.

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Anesthesia Books from Elsevier

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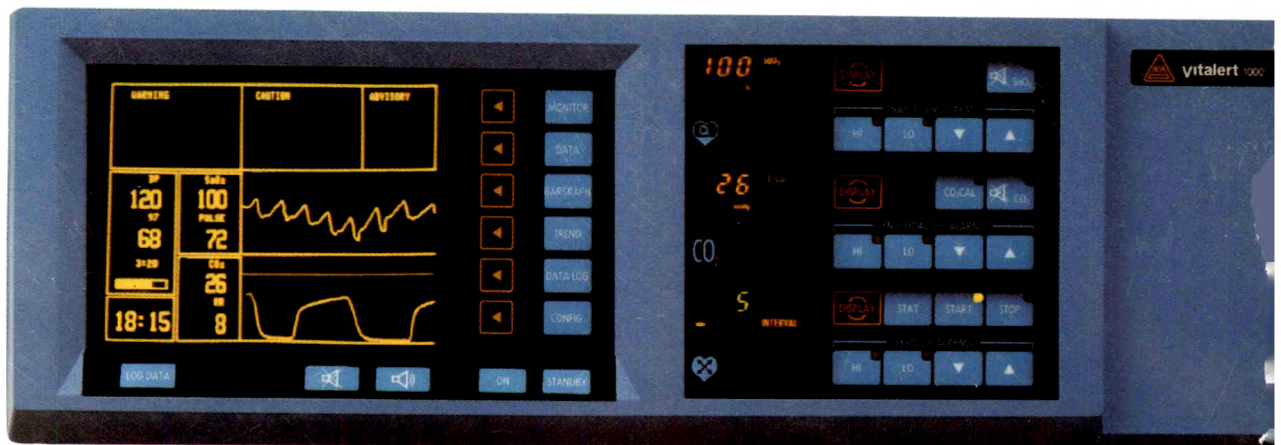
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